FORMULATION DEVELOPMENT AND *IN VITRO* EVALUATION OF GASTRO RETENTIVE FLOATING TABLETS OF BETAHISTINE HYDROCHLORIDE

A Dissertation submitted to

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY
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In partial fulfillment of the requirements for the award of degree of

MASTER OF PHARMACY IN PHARMACEUTICS

Submitted by

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Under the guidance of

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DEPARTMENT OF PHARMACEUTICS
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EVALUATION OF THESIS

This is to certify that the research work embodied in this thesis entitled **"FORMULATION DEVELOPMENT AND IN VITRO EVALUATION OF GASTRO RETENTIVE FLOATING TABLETS OF BETAHISTINE HYDROCHLORIDE"** is carried out by **Reg. No. 261211253** at College of Pharmacy, Madras Medical College is evaluated.

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This is to certify that the research work embodied in this thesis entitled **"FORMULATION DEVELOPMENT AND *IN VITRO* EVALUATION OF GASTRO RETENTIVE FLOATING TABLETS OF BETAHISTINE HYDROCHLORIDE"** is a bonafide research work done by **Reg. No. 261211253** in partial fulfillment of the requirement of the degree of Master of Pharmacy in Pharmaceutics by The Tamil Nadu Dr. M.G.R. Medical University during the academic year 2013-2014.

Dr. A. Jerad Suresh M.Pharm., Ph.D., MBA.,

Date:

Place: Chennai

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CERTIFICATE

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Prof. K. Elango M.Pharm., (Ph.D.,)

Date:

Place: Chennai

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LIST OF ABBREVIATIONS

%	Percentage
µg	microgram
BCS	Biopharmaceutics Classification System
BET	Betahistine
BPPV	Benign paroxysmal positional vertigo
CAS	Chemical Abstract Service
cm	centimeter
cps	Centipoise
CR	Contolled Release
CRDDS	Controlled Release Drug Delivery System
FDA	Food and Drug Administration
FTIR	Fourier Transform Infra-Red
g	gram
GIT	Gastrointestinal tract
GMT	Gastric emptying time
GRDDS	Gastro retentive drug delivery system
GRT	Gastro retentive time
HPMC	Hydroxypropyl methylcellulose
HPMC	Hydroxypropylmethyl cellulose
hrs	hours
MCC	Micro crystalline cellulose
mg	milligram

min	minute
mL	milliliter
mm	millimeter
N	normality
NC	no change
nm	nanometer
PVP	Poly vinyl pyrrolidone
RH	Relative Humidity
SCMC	Sodium carboxy methyl cellulose
USP	United States Pharmacopoeia
UV	Ultra-Violet

1. INTRODUCTION

INTRODUCTION:

Oral solid dosage forms:

Oral route is the most frequently used route for administration of drugs. Tablets and capsules represent the majority of dosage forms administered orally. Tablets are solid preparations each containing a single dose of one or more active substances. They are obtained by compressing uniform volumes of particles or by another suitable manufacturing technique, such as extrusion, moulding or freeze-drying (lyophilisation). Tablets are intended for oral administration. Some are swallowed whole, some after being chewed, some are dissolved or dispersed in water before being administered and some are retained in the mouth where the active substance is liberated.[1]

Tablets are usually straight, circular solid cylinders, the end surface of which are flat or convex and the edges of which may be beveled. They may have break marks and may bear a symbol or other markings. Tablets may be coated or uncoated. Tablets consists of one or more active substances with or without excipients such as diluents, binders, disintegrating agents, glidants, lubricants, substances capable of modifying the behavior of the preparation in digestive tract, colouring matter authorized by the competent authority and flavouring substances.[1]

For many disease states the ideal dosage regimen is that by which an acceptable therapeutic concentration of drug at the site(s) of action is attained immediately and is then maintained constant for the desired duration of the treatment. Therefore, ‘steady-state’ plasma concentrations of a drug can be achieved promptly and maintained by the repetitive administration of conventional oral dosage form. Although conventional oral dosage form releases the complete dosage of drug rapidly in immediate absorption into the systemic circulation, it has some severe limitations such as,

1. Drugs having short half-life require frequent administration
2. The fluctuations of drug concentration in plasma can lead to under medication or over medication.
3. The fluctuating drug concentration in plasma can lead to precipitation of adverse effects especially for a drug with small therapeutic index.

4. The typical peak-plasma concentration-time profile of immediate release makes the attainment of steady state concentration difficult.

These limitations led to the development of 'extended-release' preparations, for reducing the cyclical plasma concentrations. A variety of terms was used to describe these systems.

- Delayed release
- Repeat action
- Prolonged release
- Sustained release
- Extended release
- Controlled release
- Modified release

Delayed release:

A delayed-release dosage form is designed to release the drug at a time other than promptly after administration. The delay may be time based or based on the influence of environmental conditions like gastrointestinal pH. (E.g.) enteric-coated tablets, pulsatile-release capsules.

Repeat action:

Repeat action forms usually contain two single doses of medication, one is released fairly soon after administration and the second dose is subsequently released in an extended manner at intermittent intervals.

Prolonged release:

It provides drug absorption over a longer period of time than from a conventional dosage form. However, there is an implication that onset is delayed because of an overall slower release rate from the dosage form.

Sustained release:

It indicates an initial release of drug sufficient to provide a therapeutic dose soon after administration, and then a gradual release over an extended period.

Extended release:

It allows a reduction in dosing frequency from that necessitated by a conventional dosage forms so that plasma concentrations are maintained at a therapeutic level for a prolonged period of time (usually between 8 and 12 hours).

Controlled release:

These dosage forms release drug at a constant rate and provide plasma concentrations that remain invariant with time.

Modified release:

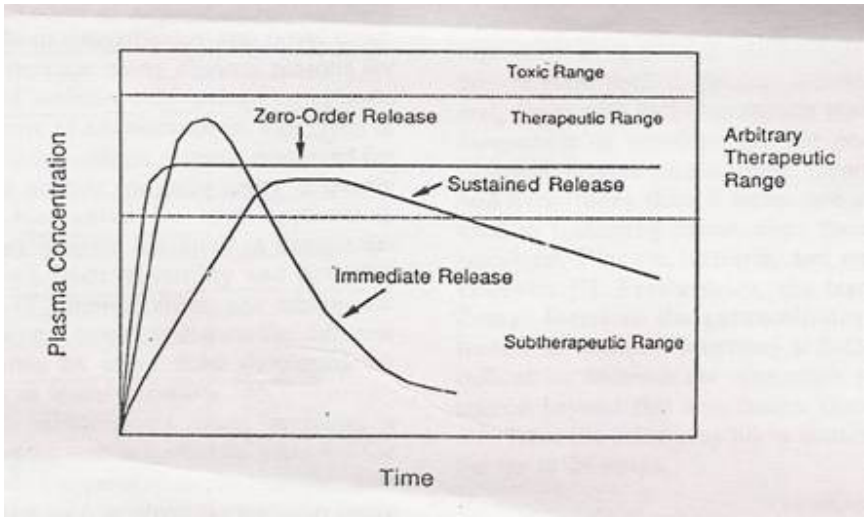
These are the dosage forms whose drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional forms.

It is interesting to note that the USP considers that the terms controlled release; prolonged release and sustained release are interchangeable with each other. From a biopharmaceutical perspective this is not strictly a concern.[2]

CONTROLLED RELEASE DRUG DELIVERY SYSTEMS: [3]

Controlled release drug delivery is one which delivers the drug at a predetermined rate locally or systemically for a specified period of time. The goal of a sustained release dosage form is to maintain therapeutic blood or tissue levels of the drug for an extended period. Sustained release dosage form that provides medication over an extended period of time. Controlled release denotes that the system is able to provide some actual therapeutic control, whether this is of temporal nature, spatial nature or both. In other words, the system attempts to control drug concentrations in the target tissue. This correctly suggests that there are sustained release systems that cannot be considered as controlled-release systems.

Fig.1.1: Plasma drug concentration – profiles for conventional release formulation, a sustained release formulation and a zero – order controlled release formulation.



In general, the goal of a sustained release dosage form is to maintain therapeutic blood or tissue levels of the drug for an extended period. This is usually accomplished by attempting to obtain zero order release from the dosage form that is independent of the amount of the drug in the delivery system (i.e., a constant release rate).

Advantages of controlled release drug delivery systems

1. Improved patient compliance.
2. Reduction in fluctuation in steady-state levels.
3. Increased safety margin of high potency drugs due to better control of plasma levels.
4. Maximum utilization of drug enabling reduction in total amount of dose administered.
5. Better control of disease condition.
6. Reduced intensity of local or systemic side effects.

Disadvantages of controlled release drug delivery system

1. Decrease systemic availability in comparison to immediate release formulation or conventional dosage forms. This may be due to
    - Incomplete release
    - Increased first-pass metabolism

- Increased instability,
- Insufficient residence time for complete release
- Site-specific absorption
- pH dependent solubility

2. Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.
3. Reduced potential for dosage adjustment of drugs normally administered in varying strengths.
4. Higher cost of formulation.

An oral controlled-release system can be designed either as a continuous release system or as a pulsed release system.

1. Continuous release systems release drug continuously over an extended period of time.
2. Pulsatile release systems are characterized by a time period of no release followed by a rapid and complete or extended drug release.

Continuous release system can be classified into two categories-

1. Continuous-Transit systems
2. Gastro retentive systems

Oral controlled release dosage forms can be classified into different ways. One way is to distinguish between single-unit dosage forms such as tablets and capsules, and multiparticulate dosage forms such as pellets or beads. Controlled release products can be classified into[3]

- Reservoir systems
- Osmotic systems
- Ion-exchange resins
- Matrix systems

GASTRORETENTIVE DRUG DELIVERY SYSTEMS (GRDDS) [4]

Dosage form with a prolonged gastric residence and controlled drug delivery are called as GRDDS. Thus, these dosage forms significantly extend the period of time over which the drugs may be release in comparison to other controlled release drug delivery systems. Such systems have several applications and advantages-

1. Effective in delivery of sparingly soluble and insoluble drugs or drugs having low solubility at intestinal p^H e.g. diazepam.
2. Effective in the therapy of local disease such as H. *pylori* infection with drugs such as antibiotics or acidity treatment with antacids and misoprostol.
3. Suitable for administering drugs having absorption window in stomach or upper part of small intestine, e.g.gabapentin, metformin, levodopa, riboflavin, etc.
4. Suitable for administering drugs unstable in intestine or colon e.g. Captopril.
5. Enables reduction in variability in drug absorption which is commonly due to differences in gastric residence time.
6. Drugs which undergo abrupt changes in their pH dependent solubility due to factors such as food, age and pathophysiological conditions of GI tract.

Advantages

1. The bioavailability of therapeutic agents can be significantly enhanced especially for those which get metabolized in the upper GIT by this gastro retentive drug delivery approach in comparison to the administration of non-gastro retentive drug delivery.
2. For drugs with relatively short half-life, sustained release may result in a flip-flop pharmacokinetics and also enable reduced frequency of dosing with improved patient compliance.
3. They also have an advantage over their conventional system as it can be used to overcome the adversities of the gastric retention time (GRT) as well as the gastric emptying time (GET). As these systems are expected to remain buoyant on the gastric fluid without affecting the intrinsic rate of employing because their bulk density is lower than that of the gastric fluids.

4. Gastro retentive drug delivery can produce prolong and sustain release of drugs from dosage forms which avail local therapy in the stomach and small intestine. Hence they are useful in the treatment of disorders related to stomach and small intestine.
5. The controlled, slow delivery of drug form gastro retentive dosage form provides sufficient local action at the diseased site, thus minimizing or eliminating systemic exposure of drugs. This site-specific drug delivery reduces undesirable effects of side effects.
6. Gastro retentive dosage forms minimize the fluctuation of drug concentrations and effects. Therefore, concentration dependent adverse effects that are associated with peak concentrations can be presented. This feature is of special importance for drug with a narrow therapeutic index.
7. Gastro retentive drug delivery can minimize the counter activity of the body leading to higher drug efficiency.
8. Reduction of fluctuation in drug concentration makes it possible to obtain improved selectivity in receptor activation.
9. The sustained mode of drug release from Gastro retentive doses form enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the chemical outcomes.

Disadvantages

1. These require sufficiently high levels of stomach fluids, for the system to float and to work efficiently.
2. Not suitable for drugs with stability or solubility problem in stomach.
3. Drugs which undergo extensive first pass metabolism are not suitable candidates.
4. Drugs with irritant effect also limit the applicability.

Requirements for the gastro retentive formulations

1. It must form a cohesive gel barrier to facilitate retention.
2. It must maintain specific gravity lower than gastric contents.
3. It should release contents slowly to serve as a reservoir.

The strategies for delaying drug transit through the GIT fall into one of three categories-

1. Pharmacological approach: involves co-administration or incorporation of a drug into the dosage form that delays either gastric emptying e.g. antimuscarinic agents such as propantheline or a drug that retards gastric motility e.g. loperamide.
2. Physiological approach: use of natural materials or fat derivatives such as triethanolamine myristate which stimulate the duodenal receptors to slow gastric emptying. Use of large amounts of volume filling polymer such as polycarbophil can slow gastric emptying.
3. Pharmaceutical approach: the first two approaches are not used because of toxicity problems. The various pharmaceutical approaches or systems used for gastroretention can be classified as-
    a. Floating systems
    b. Swelling and expanding systems
    c. Bioadhesive systems
    d. Modified shape systems
    e. High density systems

GASTRIC EMPTYING AND PROBLEMS

The stomach is anatomically divided into three parts

1. Fundus
2. Body
3. Antrum (pylorus)

The process of gastric emptying occurs both during fasting and fed states. The pattern of motility differs markedly in the two states. In the fasted state, it is characterized by an interdigestive series of electrical events which cycle both through the stomach and small intestine every 2-3 h. This activity is called the interdigestive myoelectric cycle or migrating myoelectric complex (MMC), which is often divided into four consecutive phases.

Phase-I lasts 45-60 min, is quiescent, with rare low amplitude contractions.

Phase-II with a length of 30-45 min has intermediate amplitude contractions & involves bile secretion.

Phase-III is also termed 'housekeeper wave' & extends for 5-15 min.

Phase-IV has a length of less than 5 min & connects between the maximal amplitude contractions to the basal phase.

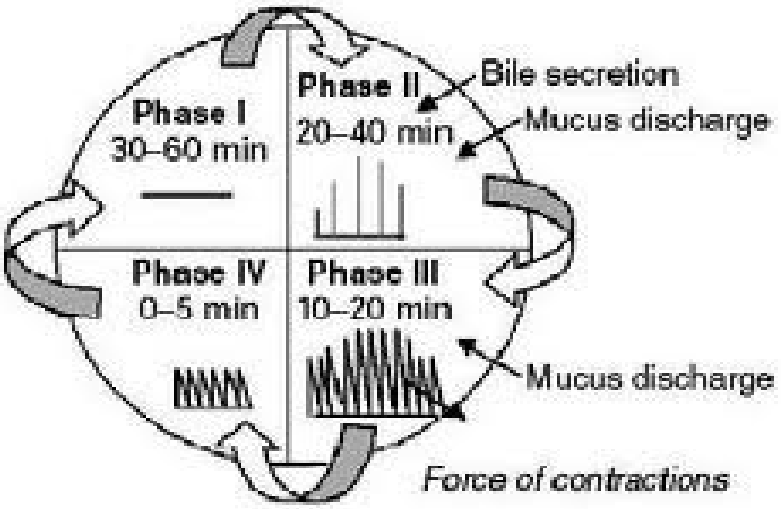


Fig 1.2: Phases of migrating myoelectric complex

Factors affecting gastric retention

Density, size, shape of dosage form, concomitant intake of food and drugs such as anticholinergic agents(e.g., atropine, propantheline), opiates(e.g., codeine) and prokinetic agents (e.g.,metoclopramide, cisapride), and biological factors such as gender, posture, age, body mass index, and disease states(e.g., diabetes, Crohn's disease)

1. Density

The density of a dosage form also affects the gastric emptying rate and determines the location of the system in the stomach. Dosage forms having a density lower than the gastric contents can float to the surface, while high density systems sink to bottom of the stomach.

Both positions may isolate the dosage system from the pylorus. A density of < 1.0 gm/ cm^3 is required to exhibit floating property.

2. Food

Food affects the GRT of dosage forms depending on its nature, caloric content, and the frequency of intake. Nature of meal-feeding of indigestible polymers or fatty acid salts can change the motility pattern of stomach to a fed-state, thus decreasing the gastric emptying rate and prolonging drug release. Caloric content-GRT can be increased by 4-10 hours with a meal that is high in proteins and fats. Frequency of feed- The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of myoelectric motor complex.

3. Size

Small-size tablets are emptied from the stomach during the digestive phase, while larger units are expelled during housekeeper waves. Floating units with a diameter equal to or less than 7.5mm had longer GRTs compared to non-floating units. GRT were similar for floating and non-floating units having a larger diameter of 9.9mm.

4. Shape

Ring-shaped and tetrahedron-shaped devices have a better gastric residence time as compared with other shapes.

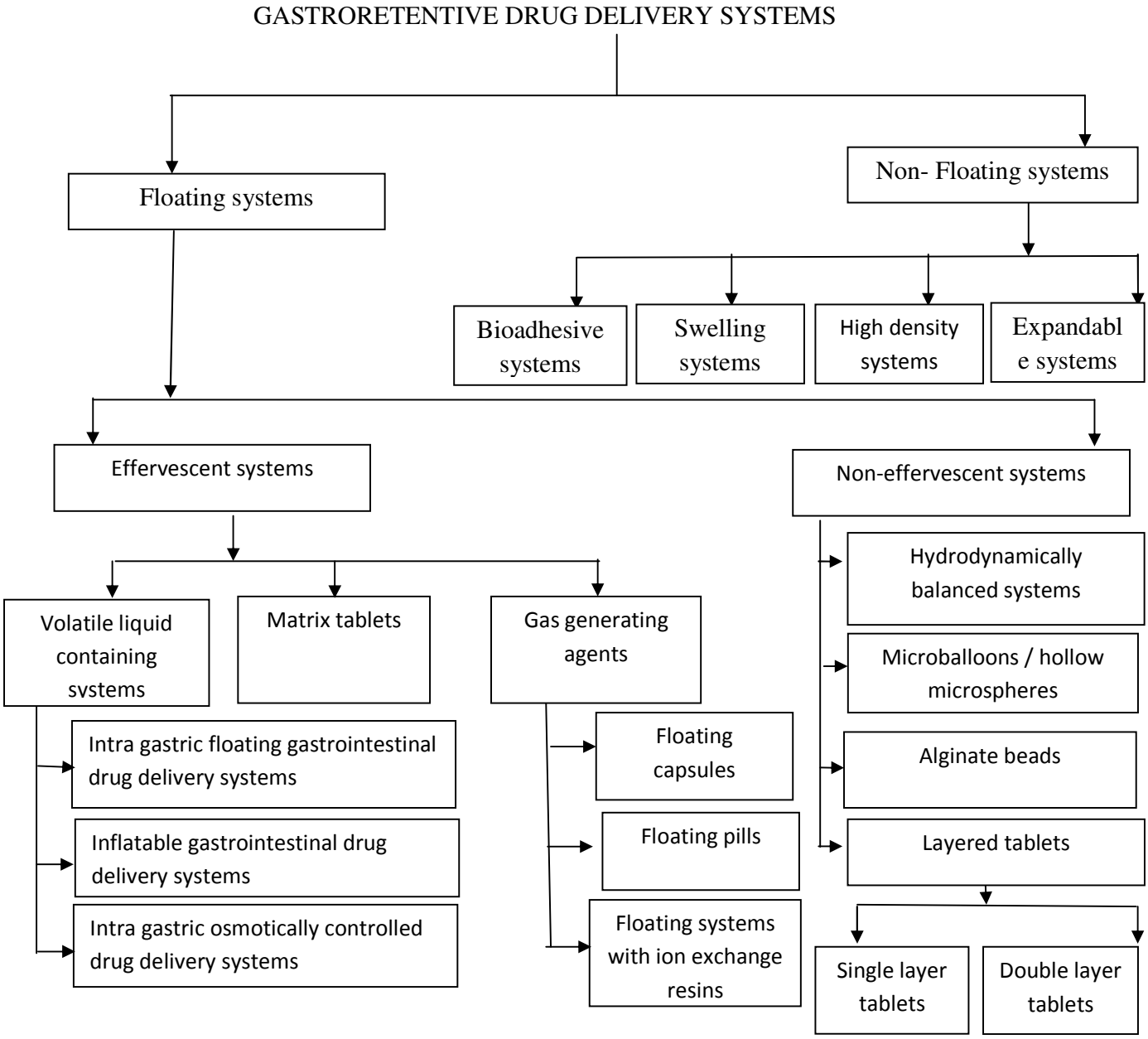
5. Gender

Mean ambulatory GRT in males (3.4±0.6 hours) is less compared with their age and race matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.

6. Fed or unfed state

Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

7. Age – elderly people, especially those over 70, have a significantly longer GRT[4]


GASTRORETENTIVE DRUG DELIVERY SYSTEMS
Floating systems
Non- Floating systems
Bioadhesive systems
Swelling systems
High density systems
Expandable systems
Effervescent systems
Non-effervescent systems
Volatile liquid containing svstems
Matrix tablets
Gas generating agents
Hydrodynamically balanced systems
Microballoons / hollow microspheres
Alginate beads
Layered tablets
Intra gastric floating gastrointestinal drug delivery systems
Inflatable gastrointestinal drug delivery systems
Intra gastric osmotically controlled drug delivery systems
Floating capsules
Floating pills
Floating systems with ion exchange resins
Single layer tablets
Double layer tablets

APPROACHES TO GASTRIC RETENTION[4]

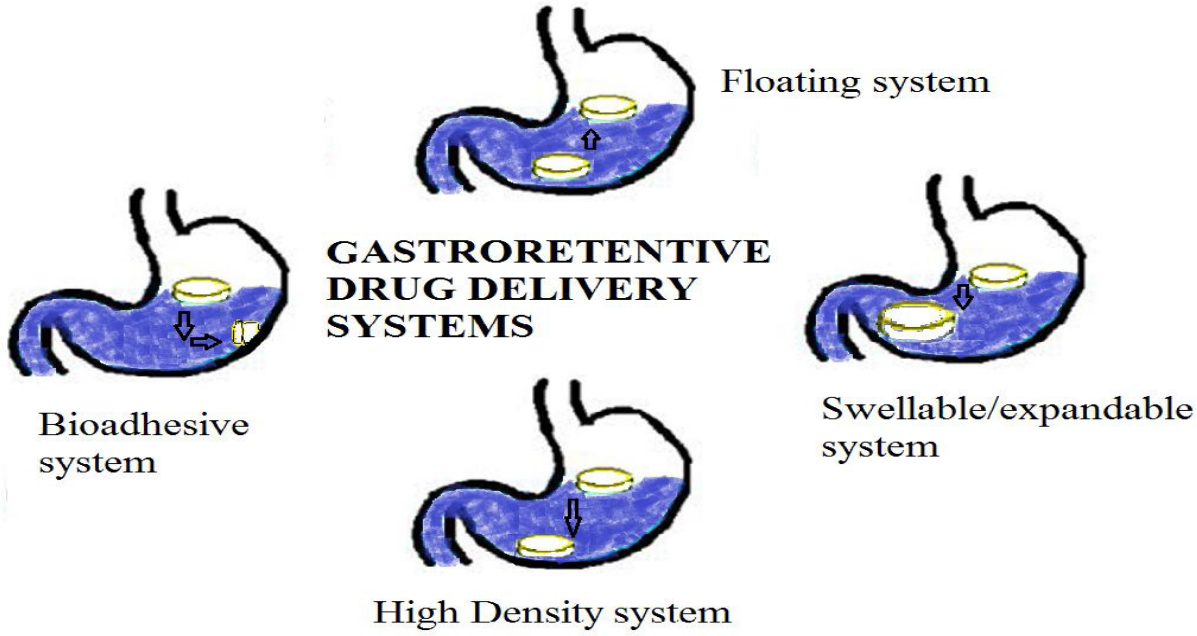


Fig.1.3: showing various approaches for gastro retentive drug delivery systems

FLOATING DRUG DELIVERY SYSTEMS[4]

Floating drug delivery system or hydrodynamically balanced systems have a bulk density lower than gastric contents and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in plasma drug concentrations. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus used for determination of resultant weight (RW). The RW apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if RW is on the higher positive side. Based on the buoyancy mechanism, floating systems are classified as follows

1. Effervescent systems
2. Non-Effervescent systems

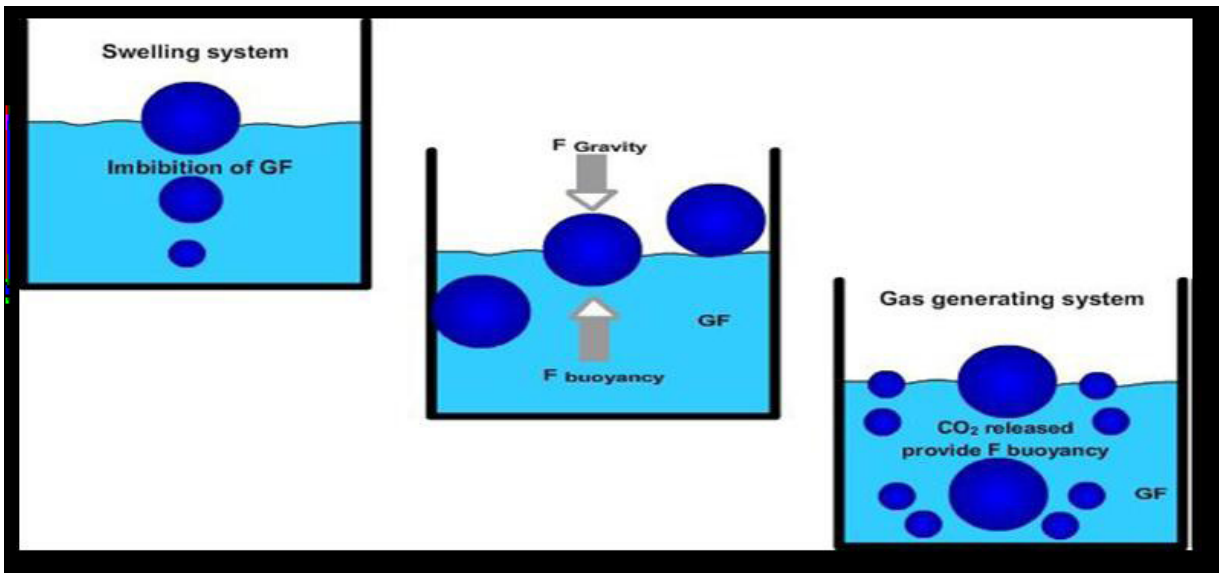


Fig. 1.4: Mechanism of floating drug delivery systems

The magnitude and direction of force/resultant weight (up or down) is corresponding to its buoyancy force ($F_{buoyancy}$) and gravity force ($F_{gravity}$) acting on dosage form

$$F = F_{buoyancy} - F_{gravity}$$

$$F = D_f g V - Ds\ g\ V$$

$$F = (D_f - Ds)\ g\ V$$

$$F = (D_f - M/V)\ g\ V$$

Where,

F = resultant weight of object

D_f = Density of Fluid

DS = Density of Solid object

g = Gravitational force

M = Mass of dosage form

V = Volume of dosage form

So when Ds, density of dosage form is lower, F force is positive gives buoyancy and when it is Ds is higher, F will negative shows sinking.

Plot of F vs. Time is drawn and floating time is time when F approaches to zero from positive values.

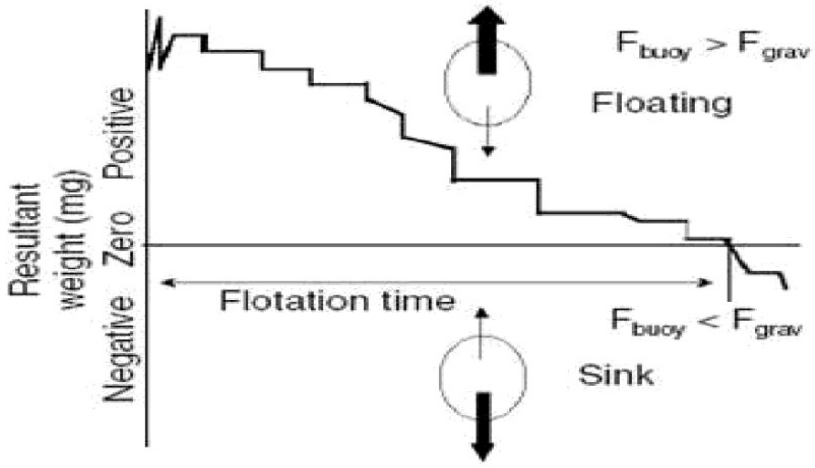


Fig.1.5: Effect of buoyancy force and gravity force on drug delivery system

Effervescent (gas generating) systems

Floatability can be achieved by generation of gas bubbles. These buoyant systems utilize matrices prepared with swellable polymers such as polysaccharides (e.g. chitosan), effervescent Components (e.g. sodium bicarbonate, citric acid or tartaric acid). The optimal stoicheometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76: 1. In this system carbon dioxide is released and causes the formulation to float in the stomach. Other approaches and materials that have been reported are a mixture of sodium alginate and sodium bicarbonate, multiple unit floating dosage forms that generate gas (carbon dioxide) when ingested, floating mini capsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone (PVP) coated with hydroxyl propyl methylcellulose (HPMC), and floating system based on ion exchange resin technology. Bilayer or multilayer system has also been designed. Drugs and excipients can be formulated independently and the gas generating material can be incorporated into any of the layers. Further modifications involve coating of the matrix with a polymer which is permeable to water, but not to carbon dioxide[4].

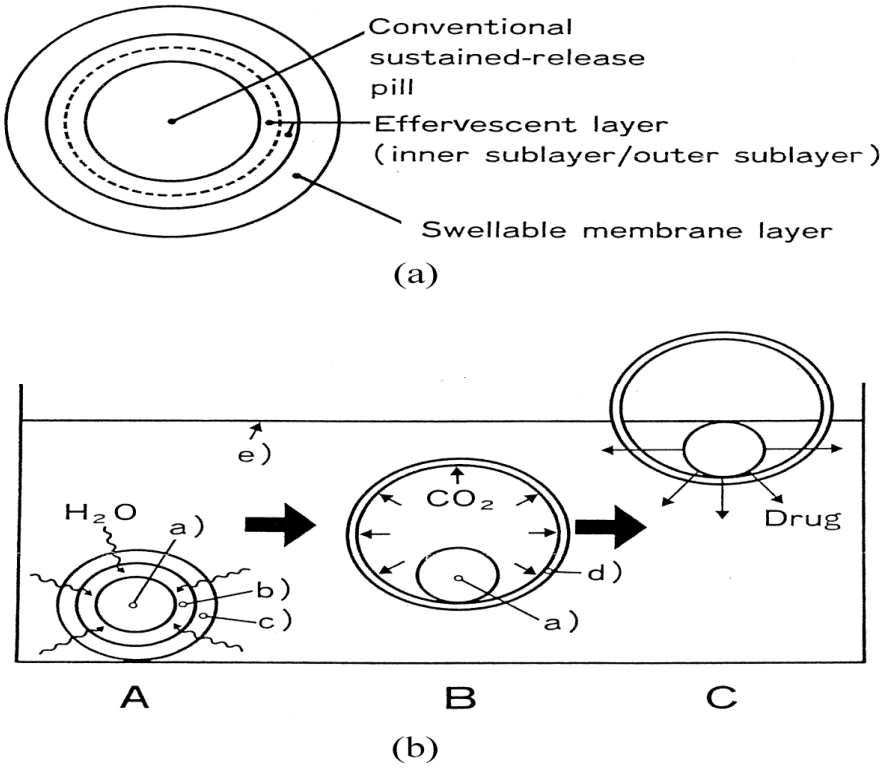


Fig. 1.6: (a) multiple unit oral floating dosage system (b) stages of floating mechanism

A. Penetration of water B. Generation of carbon dioxide and floating C. Dissolution of drug

These systems are further classified as below.

1. Volatile liquid containing systems

   These are further categorized as

   A. Intragastric floating gastrointestinal drug delivery system: This system contains a floatation chamber which contains vacuum or an inert, harmless gas and a microporous compartment enclosing drug reservoir.

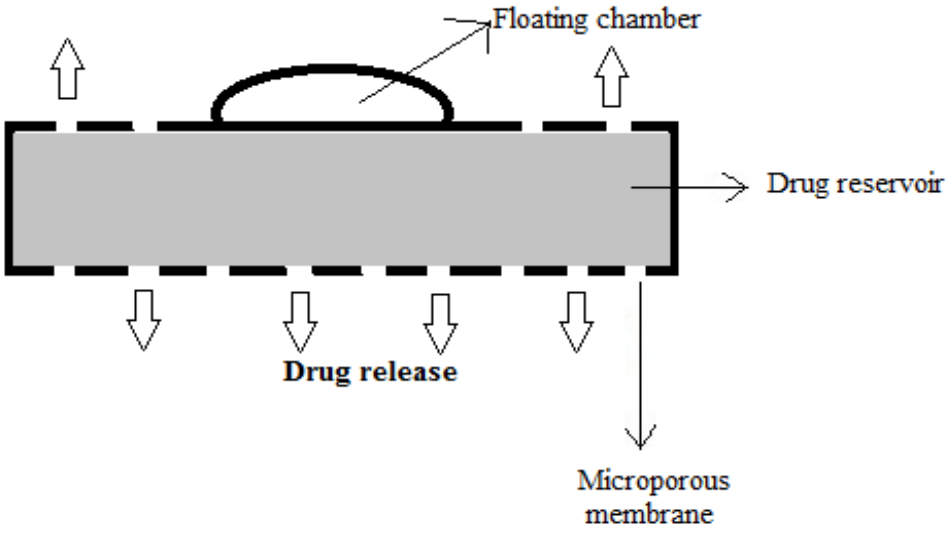


Fig.1.7: showing intragastric floating gastrointestinal drug delivery system

B. Inflatable gastrointestinal delivery system: These systems possess inflatable chamber containing liquid ether which gasifies at body temperature to inflate the stomach. Inflatable chamber contains bioerodible polymer filament (e.g., copolymer of polyvinyl alcohol and polyethylene) that gradually dissolves in gastric fluid and finally causes inflatable chamber to release gas and collapse.

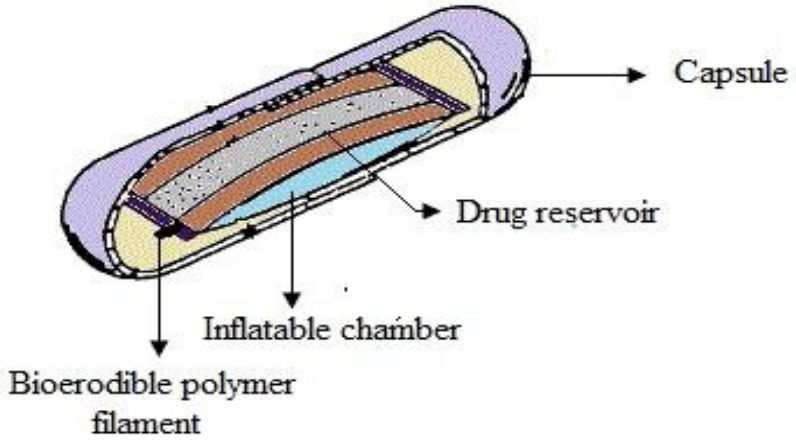


Fig.1.8: showing inflatable gastrointestinal drug delivery systems

C. Intragastric-osmotically controlled drug delivery system: It is composed of osmotic pressure controlled drug delivery device and an inflatable floating capsule. In the stomach, inflatable capsule disintegrates and releases the osmotically controlled drug delivery system which contains two components; drug reservoir compartment and osmotically active compartment[5].

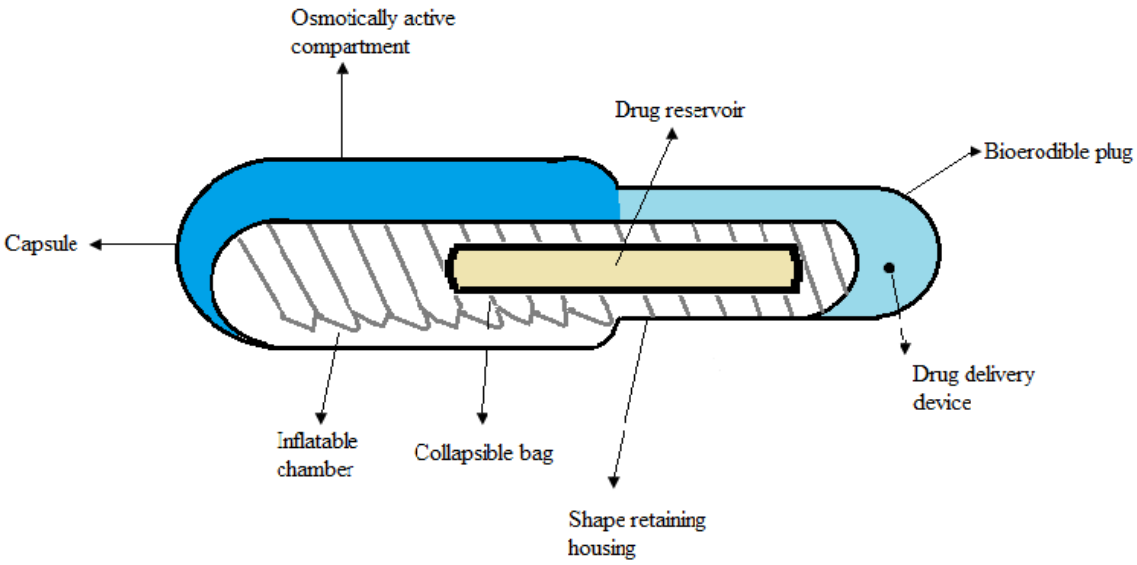


Fig.1.9: showing Intragastric osmotically controlled drug delivery systems

2. Matrix tablets

It may be formulated as a single layer matrix tablet by incorporating bicarbonates in matrix forming hydocolloid gelling agent or a bilayer matrix tablet with gas generating matrix as one layer and drug being the second layer. It can also be formulated as triple layer matrix tablet with gas generating matrix as one layer and 2 drug layers.

3. Gas generating systems

These systems utilize effervescent compounds like sodium bicarbonate, citric acid and tartaric acid. It is further divided as follows.

A. Floating capsules: These are prepared by formulating mixture of sodium bicarbonate and sodium alginate. On exposure to acidic environment, carbon dioxide gas is generated which is trapped in the hydrating gel network and makes the system to float.

B. Floating pills: These are a type of sustained release formulations which are basically multiple unit type of dosage forms. The sustained release pill is surrounded by two layers. Outer layer consists of swellable membrane and the inner layer consists of effervescent agents. The system swells due to swellable membrane and then sinks. Due to presence of effervescent agents, CO_2 is released and the system floats.

C. Floating systems with ion exchange resins: The most common approach for formulating these systems involves resin beads loaded with bicarbonate. This is then coated with ethyl cellulose which is usually insoluble but permeable to water. This causes carbon dioxide to release and the system to float.

Non effervescent FDDS

Non-effervescent floating drug delivery systems are normally prepared from gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides or matrix forming polymers like polyacrylate, polycarbonate, polystyrene and polymethacrylate. In one approach, intimate mixing of drug with a gel forming hydrocolloid which results in contact with gastric fluid after oral administration and maintain a relative integrity of shape and a bulk density less than unity within the gastric environment. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Excipients used most commonly in these systems include hydroxy propyl methylcellulose (HPMC) polyacrylates, polyvinyl acetate, carbopolagar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates. These are further classified as follows

1. Hydrodynamically balanced drug delivery systems

These systems contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. These are single-unit dosage form, containing one or more gel-forming hydrophilic polymers. Hydroxy propyl methylcellulose (HPMC), hydroxyl ethyl cellulose (HEC), hydroxyl propyl cellulose (HPC), sodium carboxymethyl cellulose (NaCMC), polycarbophil, polyacrylate, polystyrene, agar, carrageenans or alginic acid are commonly used excipients to develop these systems. The polymer is mixed with drugs and usually administered in hydrodynamically balanced system capsule. The capsule shell dissolves in contact with water and mixture swells to form a gelatinous barrier, which imparts buoyancy to dosage form in gastric juice for a long period. Continuous erosion of the surface

allows water penetration to the inner layers, maintaining surface hydration and buoyancy to dosage form. Incorporation of fatty excipients gives low-density formulations reducing the erosion. Effective drug deliveries depend on the balance of drug loading and the effect of polymer on its release profile.

2. Microballoons / hollow microspheres

These systems contain outer polymer shell loaded with drug. The outer polymer shell is made up of polymers like polycarbonate, cellulose acetate, calcium alginate, agar, etc. Buoyancy lag time and drug release from the system is dependent on the quantity of polymers used in the formulation. These are prepared by emulsion-solvent diffusion method.

3. Alginate beads

These are formulated using calcium and low methoxylated pectin or calcium low methoxylated pectin and sodium alginate. In this type, sodium alginate solution is added to aqueous solution of calcium chloride which causes precipitation of calcium alginate (beads). These beads are then separated and dried by air convection and freeze dried. This results in the formation of a porous system which remains buoyant in the stomach.

4. Layered tablets

These may be of single layer or double layered.

A. Single layered floating tablets: This type of tablets contain drug mixed with gel forming hydrocolloids and other excipients. Upon contact with gastric fluids, the hydrocolloids swell and maintain bulk density less than one and hence remain buoyant in the stomach.

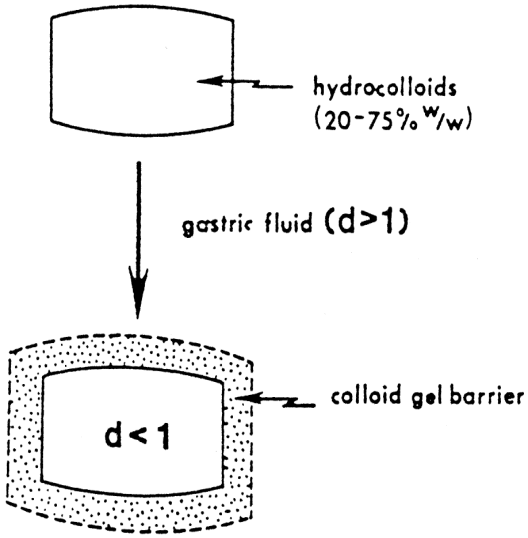


Fig. 1.10: intra gastric floating tablet

B. Double layered floating tablets: This type of tablets contains two layers. One of which is immediate releasing layer and the other is sustained release layer containing drug and hydrocolloids which remains in the stomach for a prolonged period of time.

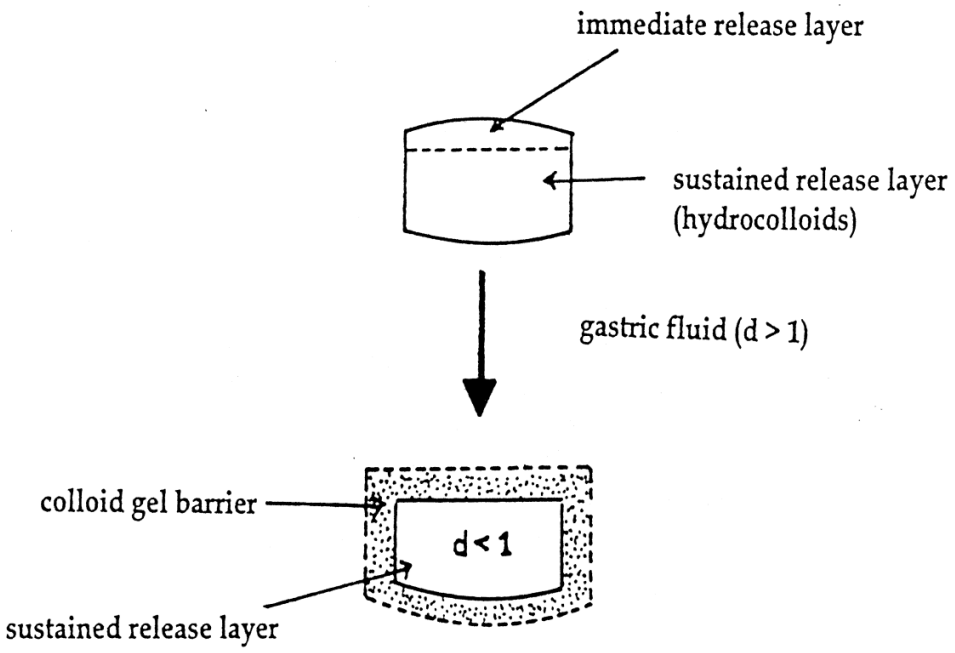


Fig.1.11: Intragastric floating bilayer tablet

NON-FLOATING SYSTEMS

These are another class of gastroretentive drug delivery systems which do not float but remain in the stomach for a prolonged time period. These systems are formulated by any of the following approaches.

1. Bioadhesive systems: These types of systems adhere to the biological membrane (mucosa) of the stomach and maintain intimate contact with the membrane for a longer time and hence retains in stomach for its prolonged release. These systems are formulated using bioadhesive polymers which can adhere to epithelial surface in the stomach. Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan, CMC and gliadin, etc.
2. Swelling systems: These are a type of non-floating gastro retentive drug delivery system which when enters stomach swells (due to presence of swellable polymers) to an extent that cannot pass through the pyloric sphincter leading to its retention in the stomach.
3. High density systems: These systems possess density greater than the gastric fluids due to which the system sinks to the bottom and remains in the stomach. These are formulated by coating drug on heavy inert materials like zinc oxide, titanium dioxide, iron powder, etc.
4. Expandable systems: These systems are capable of expanding and retain in the stomach for longer periods. These are usually formulated as a capsule containing dosage form in folded and compact form. After being exposed to stomach environment, capsule shell disintegrates and dosage form expands preventing its exit through the stomach. By using a suitable polymer, sustained and controlled drug delivery can be achieved.
5. Evaluation of gastro retentive dosage forms
6. Evaluation for gastro retention is carried out by means of X-ray and or gamma scintigraphic monitoring of dosage form transit in the GI tract[4].

Tab.1.1: Gastro retentive products available in the market

Brand name	Active ingredient
Cifran OD®	Ciprofloxacin
Madopar®	L-dopa & Benserazide
Valrelease®	Diazepam
Topalkan®	Aluminium-Magnesium antacid
Liquid Gavison®	Aluminum hydroxide
Almagate flatcoat®	Aluminium-Magnesium antacid
Conviron®	Ferrous sulphate
Cytotec®	Misoprostol

Tab.1.2: Commonly used drug in formulation of gastro retentive dosage forms

Dosage forms	Drugs
Floating tablets	Acetaminophen, acetylsalicylic acid, ampicillin, amoxicillin trihydrate, Atenolol, Captopril, cinnerezine, Chlorpheniramine maleate, ciprofloxacin, diltiazem, Isosorbide mononitrate, Para amino benzoic acid, prednisolone, nimodipine, sotalol, Theophylline, verapamil
Floating capsules	Chlordiazepoxide hydrochloride, diazepam, furosemide, L-dopa and Benserazide, nicardipine, misoprostol, Propranolol, pepstatin
Floating microspheres	Aspirin , griseofulvin, P-nitro aniline, ibuprofen, terfenadine, tranilast
Floating granules	Diclofenac sodium, indomethacin, prednisolone

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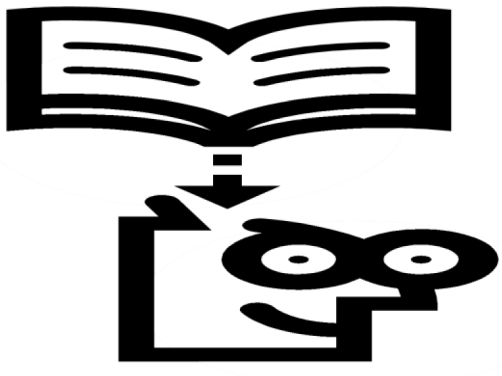


2. REVIEW OF LITERATURE

REVIEW OF LITERATURE

M.Parvathi[6] formulated and evaluated floating tablets of metformin hydrochloride composed of HPMC K 100 and gellan gum by wet granulation method. The developed floating tablets of Metformin hydrochloride showed prolonged drug release for at least 12 hrs, thereby improving the bioavailability and patient compliance.

C.Bijumol et al.,[7] formulated and evaluated floating tablets of theophylline using gel forming hydrophilic polymers such as HPMC K4M, HPMC K100M and HPMC 15 cps. Formulations with HPMC K100M & HPMC K4M showed better buoyancy, control of drug release and the drug release was similar to that of marketed product.

K.Ravishankar et al.,[8] formulated and evaluated Ciprofloxacin floating tablets using different polymer like HPMC K4M, SCMC and carbopol 934 by direct compression technique. The experimental results revealed that all formulated tablets were of good quality with regard to hardness (3.7 - 4 kg/cm2), thickness (0.3 – 0.35 cm), density (~ 1 g/cm3), weight variation (1.3- 4.2) and drug content (>90%). As the result of floating capability study increasing the effervescent base of tablets from 5% to 10% significantly lower the lag time of floating (From about 6 min to 1.5 min) as well as floating duration (From about 21 hrs to 10 hrs). *Invitro* drug release showed that all formulation released 80% of the ciprofloxacin hydrochloride in 12 hrs study period. It was found that all the formulations were statistically significant ($p \leq 0.05$).

Ara N. Patel et al.,[9] formulated and evaluated Diltiazem floating tablets were formulated with different concentrations of two grades of HPMC polymers (HPMC K4M and HPMC K100M) by using wet granulation technique. In-vitro drug release studies were performed and drug release kinetics evaluated using the linear regression method was found to follow both Higuchi and Korsemeyer and Peppas' equation. The drug release mechanism was found Fickian type in most of the formulations. The formulation containing (HPMC K 4 M) shows maximum percentage of drug release (99.87 %) and prolonged release for time period of about 12 h, thereby improves the bioavailability and patient compliance.

Md. Nazmul Hussain et al.,[10] formulated and evaluated Gastro retentive floating tablet of Simvastatin using hydrophilic rate retardant by direct compression technique using Methocel K4M as the rate controlling polymer. Methocel K4M was evaluated for its gel forming and release controlling properties. Sodium bicarbonate and citric acid were incorporated as gas generating agents. The drug release study was evaluated for eight hours using 0.1N HCl. The release mechanisms were explored and explained with zero order, first order, Higuchi, Hixon Crowell and Korsmeyer equations. It was found that the mean dissolution time, percentage drug release, release rate constant and diffusion exponent were influenced significantly by the amount of polymer incorporation.

M Seth et al.,[11] designed and characterized of floating tablets of an anti-diabetic drug. The objective of the study was to formulate and evaluate floating tablet of Pioglitazone employing guar gum, a natural gum in comparison to gellan gum which is also a natural polymer. Sodium bicarbonate was added as gas generating agent. Addition of bees wax was significantly enhanced the buoyancy of the tablets formulated with both the two polymers. The results of in vitro drug release studies showed that optimized formulation could release the drug for more than 12 hrs and remain buoyant for 12 hrs.

CH.Swarna Kamala Chinthala et al.,[12] formulated and evaluated gastro retentive floating tablets of gabapentin using effervescent technology containing gabapentin in the form of tablets using polymers like HPMC K100M, HPMC K15M, Polyox WSR 303 and sodium bicarbonate as gas generating agent. At all the strengths of the polymer tested combination of HPMC K100M and POLYOX WSR 303 (2:1) gave relatively slow release of gabapentin over 24 h when compared to other formulations. The in vitro data is fitted in to different kinetic models and the best-fit was achieved with the Higuchi model. The optimized formulation followed first order release kinetics followed by non fickian diffusion.

Sandeep Kumar G et al.,[13] formulated and evaluated gastro retentive floating tablets of Cefuroxime axetil. The low bioavailability (30-40%) and short biological half-life (1.5 hours) of Cefuroxime axetil following oral administration favours development of a gastro retentive formulation. Gastro retentive floating matrix tablets of Cefuroxime axetil were successfully

prepared with hydrophilic polymers like HPMC K4M and HPMC K15M. From the Preformulation studies for drug excipients compatibility it was observed that there was no compatability problem with the excipients used in study. The drug release from most of the formulations follows fickian diffusion. From *in vivo* X-ray studies, it was clearly observed that the floating tablets showed a gastric residence of nearby 6 hrs in fed state.

Prasad K. Lende et al.,[14] carried out formulation optimization and *in-vitro* evaluation of floating tablet of Stavudine containing HPMC K100M and Xanthan gum as release retardant polymers were studied. Sodium bi-carbonate and citric acid are used as gas generating agents. The tablets were prepared by direct compression method. Optimization was done by using design expert 8.0.4.1 and optimized formulation of stavudine floating tablet shows no significant change in hardness, drug content, floating lag time and % cumulative drug release pattern after the stability period of 3 months at 40^0C/75% relative humidity.

Chandrasekhara Rao Baru et al., [15] formulated and evaluated Ibuprofen floating tablets using various polymers like HPMC K4M and Carbopol 940 to enhance the bioavailability and therapeutic efficacy of ibuprofen. 4 formulations (F1 to F4) floating tablets of Ibuprofen were prepared using variable concentrations of HPMC E5M and Carbopol 940, buoyancy lag time and the total floating time was studied for all the formulations, the compatibility evaluations were performed by DSC analysis. Studies imply that polymers are compatible with each other. There was no interaction found between polymer and drug.

Ravi Kumar et al.,[16] formulated and evaluated effervescent floating tablet of Famotidine using gas forming agents, like sodium bicarbonate, citric acid and hydrocolloids, like hydroxypropyl methylcellulose (HPMC) and carbopol 934P. The formulations were optimized for the different viscosity grades of HPMC, carbopol 934P and its concentrations and combinations. The results of the *in-vitro* release studies showed that the optimized formulation could sustain drug release (98%) for 24 h and remain buoyant for 24 hrs. The optimized formulation was subjected to various kinetic release investigations and it was found that the mechanism of drug release was predominantly diffusion with a minor contribution

from polymeric relaxation. Optimized formulation showed no significant change in physical appearance, drug content, total buoyancy time or in vitro dissolution study after storage at 45 °C/75% RH for three months.

Naresh et al.,[17] carried out formulation and characterization of effervescent floating tablets of Esomeprazole drugs using gas-forming agents, like sodium bicarbonate, citric acid. Floating tablets were prepared by wet granulation method using PVP K-30 as a binder and the other polymers include HPMC K100M, HPMC K15M and Carbopol 934 P. All the formulations showed good floating lag time i.e. less than 3 mins. The batch containing combination of HPMC 15M, HPMC K100M and Carbopol 934P showed total floating lag time more than 24 hrs. The optimized batch showed the highest swelling index among all the prepared batches (i.e. 95%).

Arunachalam A et al.,[18] designed and evaluated levofloxacin hemihydrate floating tablets by wet granulation method, using the polymer, hydroxypropyl methyl cellulose (HPMC K100M) with different amounts and other excipients and sodium bicarbonate as gas generating agent. The study aims to improve the oral bioavailability of the drug and to achieve extended retention in the stomach which may result in prolonged absorption.

J. A. Raval et al.,[19] formulated Ranitidine hydrochloride floating matrix tablets based on low density powder research described an investigation of the effects of formulation and processing parameters on a floating matrix controlled drug delivery system consisting of a poly (styrene-divinyl benzene) copolymer low density powder. The tablets were prepared using hydrophilic matrix polymers HPMC K4M, HPMC K15M, HPMC K100M, sodium alginate, psyllum, sesbania gum, guar gum, and gum acacia, with or without low density copolymer. The effect of the addition of low density copolymer and the drug release pattern were also studied. At the same time, different concentrations of low-density copolymer were taken to examine any differences in the floating lag-time of the formulation. The in vitro release mechanism was evaluated by kinetic modeling. The tablet eroded/swelled upon contact with the release medium, and the relative importance of drug diffusion, polymer swelling and tablet erosion on the resulting release patterns varied significantly with the type

of matrix forming polymer. The highly porous copolymer provided a low density and, thus, excellent in vitro floating behavior of the tablets at a concentration of 15% (w/w).

Md. Sarfaraz et al.,[20] formulated and evaluation bilayer floating tablets of Tramadol hydrochloride using release retarding polymers like hydroxypropyl methyl cellulose grades (HPMC K4M, K15M, K100M), PEO, Sodium alginate and sodium bicarbonate as gas generating agent, with a view to deliver the drug at sustained or controlled manner in gastrointestinal tract and consequently in to systemic circulation. Formulations were found uniform with respect to thickness (5.04 to 5.07 mm) and hardness (6.3 to 6.6 kg/cm^2). The friability (0.29 to 0.37%), weight variation (1.44 to 1.71%) and Drug content (98.73 to 99.23%) of different batch of tablets were found within prescribed limits. Formulation F3 selected as best formulation, shown buoyancy lag time of 39 sec, total floating time of 36 hrs and drug release of 95.90% in a period of 24 hrs. Tablets followed diffusion controlled first order kinetics and non-fickian transport of the drug.

S.Daisy chellakumarai et al.,[21] formulated and evaluated floating tablets of Ondansetron hydrochloride using various proportions of polymers such as HPMC K4M and Ethyl cellulose. This was employed to enhance the bioavailability and therapeutic efficacy of the drug. Formulation containing high HPMC K4M and ethyl cellulose showed good floating property with total floating time between 8-12 hours. The tablets were also evaluated for its hardness, friability and in-vitro evaluation test. All parameters complied with IP limits. Results of this study indicated that the combinations of hydrophilic polymers with hydrophobic polymers were suitable to optimize sustained release formulation of Ondansetron hydrochloride.

Shailesh S Chalikwar et al.,[22] carried out design, development, and in vitro characterization of floating-bioadhesive tablets of ciprofloxacin hydrochloride for biphasic release. Biphasic tablet formulation consist of, immediate release layer contained drug, disintegrant and diluent to attain the onset of action quickly and promptly. Floating-bioadhesive sustained release layer was prepared by employing 2^3 factorial designs to study the effect of different variables on its properties. Independent variables were selected as concentration of HPMC K

4M (X1), concentration of Chitosan (X2) and concentration of effervescent agent (X3) whereas % cumulative drug release (Y1), bioadhesive strength (Y2), and floating lag time (Y3) were taken as dependent variables. The prepared tablets could float within 3 min and remain buoyant for more than 12 hrs. Biphasic release tablet showed satisfactory results with profound effect of independent variables on dependent variables, and followed zero order kinetics for 12 hrs with non-Fickian diffusion transport with swelling mechanism.

Priti Tagde et al.,[23] Formulated & evaluated bilayer floating tablets of metoprolol tartrate using disintegrant starch for the fast release layer and HPMC K grade polymers for the sustaining layer. In vitro dissolution studies were carried out in an Indian Pharmacopoeia dissolution testing apparatus I (paddle method). The formulations gave an initial burst effect to provide the loading dose of the drug followed by sustained release for 12 h from the sustaining layer of matrix embedded tablets. The *In-vitro* release study of this tablet indicated sustained release for Metoprolol tartrate and followed zero order release and 95% drug in 24hrs *in vitro* and it follow Fickian diffusion.

Neeraj Kumar Fuloria et al.,[24] designed and evaluated gastric floating matrix tablets of an anti-hypertensive drug perindropil erbumine by direct compression method. Tablets were prepared by using various grades of Hydroxylpropylmethyl cellulose i.e., HPMC K4M, HPMC K15M. Sodium bicarbonate and citric acid was incorporated as a gas generating agents. The buoyancy lag time was found less than 1 minute for all the prepared tablets and affected by viscosity of the polymers and their concentrations. The total floating time for different formulations was in the range of 12-14 hrs. The present work concludes that, floating tablets of Perindropil Erbumine showed promising result and there exist a scope for *in vivo* evaluation using suitable animal model.

J Padmavathy et al.,[25] Formulated and evaluated ofloxacin floating tablets using HPMC. Floating tablets of ofloxacin was shown controlled release thereby proper duration of action at a particular site and are designed to prolong the gastric residence time after oral administration. Different formulations were formulated by wet granulation technique using

HMC K4M, HPMC K15M and HPMC K100M (floating agent) as polymers along with sodium bicarbonate as gas generating agent. The formulations were evaluated for their physicochemical properties, buoyancy lag time, total floating time, swelling index and in vitro drug release. It was found that the hardness of the tablets affects the buoyancy characteristic of the dosage form. All formulation possessed good floating properties with total floating time between 8-12 hrs.

Rajendra Jangde et.al.,[26] formulated monolithic floating tablets of Nimesulide. The polymer used were HPMC (low & High viscosity), gaur gum, carbopol along with sodium bicarbonate as the gas generating agents. The prepared tablets were evaluated their physicochemical properties and drug release. In-vitro release studies indicated that the nimesulide release from the floating dosage form was uniform & followed zero order release. The incorporation of guar gum helps to maintain the devices integrity and due to its viscosity property also affect the drugs release profile. Sodium bicarbonate which was used as the gas-generating agents causes the tablets to floats the required time>24hrs.

Krunal patel M et.al.,[27] Prepared and evaluated gastro retentive floating tablets of mebendazole. The purpose of this research was to prepare a gastro retentive drug delivery system of Mebendazole. Chitosan and hydroxypropyl methyl cellulose of various viscosity were used. Sodium bicarbonate was incorporated as a gas generating agent. The effects of citric acid and stearic acid on drug release profile and floating properties were investigated. The addition of stearic acid reduces the drug dissolution due to its hydrophobic nature. The specific study was carried out to formulate such a dosage form that can neutralize the acidity locally in the stomach. The granulation was formed by fluidized bed processor in which top spray technique was adopted for forming the granules.

Jaimini Manish et al.,[28] formulated and evaluated effervescent floating matrix tablet of Losartan potassium. Delayed release tablets of Losartan potassium were formulated using two different grades of methocel K100 and K15 by effervescent technique. Sodium bicarbonate was employed as gas generating agent. All the prepared tablets showed good in-vitro buoyancy. A combination of sodium bi carbonate and citric acid was found to achieve

optimum in vitro buoyancy. It was observed that tablet remain float for 8-10 hrs. The tablets with high grades of methocel (K100) were found to float for longer duration as compared with formulations containing methocel K15M. It is evident from this investigation that gas powered floating matrix tablet could be promising delivery system for Losartan potassium with sustained release action.

Shweta Sharma et al.,[29] formulated captopril floating matrix tablets using different polymers as release retarding agent employing various grades of HPMC in varying ratios to formulate the floating tablets. Lactose was used as a diluent in the preparation of the tablets. Sodium bicarbonate was incorporated into the tablets to aid buoyancy of the tablets. It was concluded that the formulation F1 is the best formulations as the extent of drug release was found to be around 85%. This batch also showed immediate floatation and floatation duration of more than 8hr. The drug release model of this formulation complies with zero order kinetics.

Roughe N et al.,[30] conducted a study to evaluate the factors that improves the *in vitro* buoyancy and drug release profile of floating mini tablets containing either Piretinide or Atenolol as the model drug. The buoyancy of the minitablets were achieved either by the swelling of the excipients or by incorporating gas generating agent, sodium bicarbonate. The study concluded that it was possible to produce mini tablets containing either Piretinide or Atenolol, which have a positive resultant weight during more than 6 hrs and satisfactory release profiles.

Ingani HM, et al.,[31] described the formulation, dissolution, buoyancy and *in vivo* release tests of a double layer, sustained release Riboflavin phosphate sodium hydrophosphate matrix oral tablet containing a carbon dioxide generating layer. The in vivo behavior of this floating tablet was then compared to a classical hydrodynamically balanced capsule system. The floating dosage forms had increased residence time as compared to the non-floating tablet

Menon A et al.,[32] reported the formulation of a monolithic floating dosage form for Furosemide using factorial design keeping the drug to polymer ratio, polymer to polymer ratio and polymer grade as the three factors. The optimized formulation thus obtained was found to have a good *in vitro/in vivo* correlation.

Shoufeng Li et al.,[33] developed an optimized gastric floating drug delivery system for oral controlled delivery of Calcium. A central, composite Box-Wilson design for the controlled release of calcium was used with three formulation variables; HPMC loading, citric acid loading and magnesium stearate loading. All three formulation variables were found to significantly affect release properties. Only HPMC loading was found to be significant for floating properties.

Hilton AK, et al.,[34] fabricated an oral sustained release floating tablets of Amoxycillin trihydrate and carried out the *in vitro – in vivo* evaluation. From the studies, it shows that the drug slowly released in the stomach by diffusion from the floating matrix tablet and then trickles towards the proximal intestine where absorption occurs. It improved the delivery of antibiotic resulting in more uniform levels of antibiotic following less frequent oral dosing.

Ozdemir N, et al.,[35] developed floating bilayer tablet of Furosemide β-cyclodextrin inclusion complex. They determined the gastric residence time using radiographs by adding $BaSO_4$ and reported that the tablet stayed in stomach for 6 hrs. Also the bioavailability of Furosemide from floating tablet was about 1.8 times those of the conventional tablet and also significant *in vitro – in vivo* correlation was detected. Propranolol in a floating dosage form that demonstrates both rapid and sustained release properties were reported.

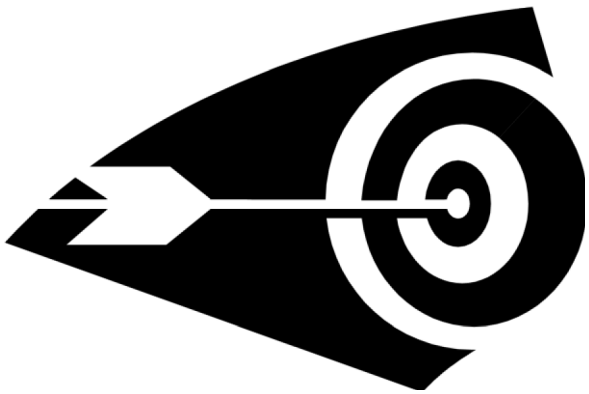
Machida S et al.,[36] fabricated two drug formulations which floated in gastric juice. One, a buoyant tablet, consisted of powdered Soyabean protein, drug and Sodium bicarbonate. The other, a laminated film type preparation consisted of a drug film, an effervescing film containing Sodium bicarbonate and outer drug release regulating time. Cinnarazine, an acid soluble drug was used as the model drug.

Jimenez-Castellanos et al.,[37] designed and tested the *in vitro* floating and bioadhesive property of Sotalol for oral application. Tablets were prepared by mixing the active ingredient with Sodium carboxy methyl cellulose, Hydroxy propyl cellulose and a carbonate to generate gas. *In vitro* tests for release of drug, floatation and bioadhesion of the tablets were carried out. They concluded that this system showed good characteristics for controlled drug delivery system.

El-Kamel et al.,[38] developed a sustained release system for Ketoprofen to increase its residence time in the stomach without contact with the mucosa and was achieved through the preparation of floating microparticles by the emulsion solvent diffusion technique. All the floating microparticle formulations were evaluated for flow properties, packability and drug release rate.

Joseph NJ, **et al**.,[39] studied the effect of solvent evaporation technique on floating type hollow polycarbonate microsphere of Piroxicam which were capable of floating on simulated gastric fluid. Pharmacokinetic analysis showed that the bioavailability of Piroxicam hollow microsphere was about 1.4 times that of free drug and was about 4.3 times for the dosage form consisting of microsphere plus the loading dose. The elimination half-life was increased by three times that of free drug.

Park, et al.,[40] developed and evaluated floating beads from Sodium Alginate solution containing CaCO3or NaHCO3as gas-forming agents with Riboflavin as a model drug. In vitro release studies revealed that $CaCO_3$ is superior to $NaHCO_3$ as gas forming agent in alginate bead preparations, with enhanced buoyancy and sustained release properties making them excellent for floating drug delivery system.



3. AIM AND PLAN OF WORK

AIM AND PLAN OF WORK

Aim of project work

1. The main objective of the present study is to develop gastro retentive floating tablets containing BET hydrochloride as sustained release for the effective treatment of vertigo.
2. To reduce frequency of administration and improve patient compliance of BET hydrochloride .

Plan of the work:

1. Preformulation Studies.
    - Physical compatibility study
    - Chemical compatibility study
2. Preparation of standard curve for BET hydrochloride.
3. Precompression studies of blends
4. Formulation of sustained release granules
5. Formulation of floating matrix tablets of BET hydrochloride using various grades of polymer of HPMC and in different proportions.
6. Post compression evaluation of tablets
    - Description
    - Uniformity of Weight
    - Hardness
    - Diameter and Thickness
    - Friability
    - Floating characteristics of tablets
    - Swelling index
    - Drug content
    - *In vitro* release study of tablets
7. Evaluation of release kinetics of optimized formulation.

4. RATIONALE OF THE STUDY

RATIONALE OF THE STUDY

Vertigo is defined as the sensation of motion, when no motion is occurring relative to the earth's gravity. It is a symptom that can be caused by disrupted activity in any part of the vestibular system or pathological conditions of other systems. The clinical course of vertigo can vary depending on the cause. Acute, severe attacks of vertigo can last from hours to days.

Vertigo is more commonly classified as taking one of three clinical courses; attacks lasting seconds or minutes (e.g.vestibular paroxysm), attacks lasting hours (e.g. Meniere's disease or vestibular migraine) or prolonged attacks lasting several days over a week (e.g. vestibular neuritis)[41,42]

Rationale for selection of drug

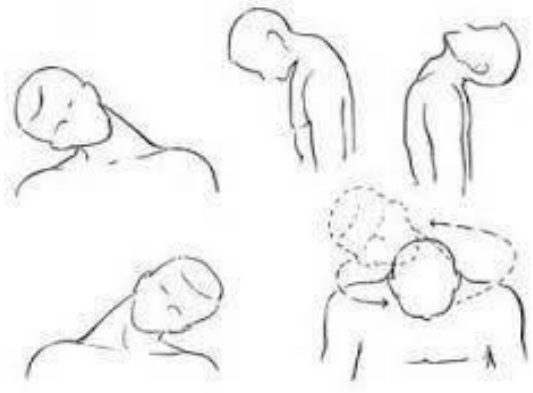
Betahistine is used to treat vertigo and exerts action by dilating blood vessel within the inner ear which can relieve pressure from excess fluid. The successful treatment of vertigo depends on the maintenance of effective drug concentration level in the body for which a constant and uniform supply of drug is desired.

BET hydrochloride is a first line treatment option for otogenic vertigo[43]. The shorter biological half-life (3-4 hours), rapid and complete absorption and the dosage of three times a day make BET hydrochloride an ideal candidate for sustained release formulations, which reduce the frequency of dose in order to improve patient compliance.[43]

Rationale for selection of dosage form

The aim of the present study is to formulate gastro retentive matrix tablets using various grades of HPMC and in different concentrations. Hydrophilic polymer matrix systems are widely used in oral drug delivery to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. Among the hydrophilic polymers, hydroxypropyl methyl cellulose derivatives are frequently used because of their nontoxic nature, easy compression, swelling properties and accommodation to high levels of drug loading.

Additionally, HPMC is a pH independent material and hence drug release from hydroxypropyl methyl cellulose matrix formulations is generally independent of processing variables.[44] Gastrointestinal resident time of the tablet vary from person to person about 8-12 hrs.[45] Floating drug delivery system is retained in the stomach for prolonged period of time and also producing sustained effect. Hence floating technique is employed for the delivery of the BET hydrochloride.



5. DISEASE PROFILE

DISEASE PROFILE

Vertigo[41-42]

Vertigo is an illusion of movement, where the patient, or the environment, seems to be moving. Imbalance always accompanies vertigo, but is not always due to vertigo and is not a synonym for vertigo.

Normal balance requires:

(a) Accurate sensory information from the eyes, proprioceptive receptors and the vestibular labyrinth (b) Coordination of this information within the brain (c) A normal motor output from the central nervous system to an intact musculoskeletal system. A fault in any of these impairs balance.

Vertigo arises if information from vestibular sources conflicts with that from the other sensory systems, or when a disordered central integration system in the brain does not correctly assess the body's movements from vestibular input. Vertigo is always a symptom of vestibular defect. This may lie in the peripheral labyrinth or in its connections within the brain. When severe it is accompanied by nausea and vomiting.

Vertigo is caused by:

(a) Peripheral vestibular disorders (labyrinthine)

(b) Spread to the labyrinth of infection from middle ear disease

(c) Central vestibular disorders, such as multiple sclerosis, tumours, infarcts

(d) External insults to the vestibular system by drugs, anaemia, hypoglycaemia, hypotension, viral infection

The commonest peripheral vestibular disorders are,

1. Menière's disease and other forms of endolymphatic hydrops,
2. Benign paroxysmal positional vertigo,

3. Sudden vestibular failure and
4. Vascular disturbances.[41]

Menière's disease

This is a disorder of endolymph control associated with dilatation of the endolymphatic spaces of the membranous labyrinth. Dilatation, or endolymphatic hydrops, may be caused by disorders of the otic capsule, but in Menière's disease it is, by definition, idiopathic. The disease usually affects only one ear, first producing symptoms between the ages of 30 and 60. It is characterised by vertigo, fluctuating hearing loss, tinnitus and sense of pressure in the involved ear. Vertigo is of sudden onset, lasts for a few minutes to 24 hours or so.

Pathology

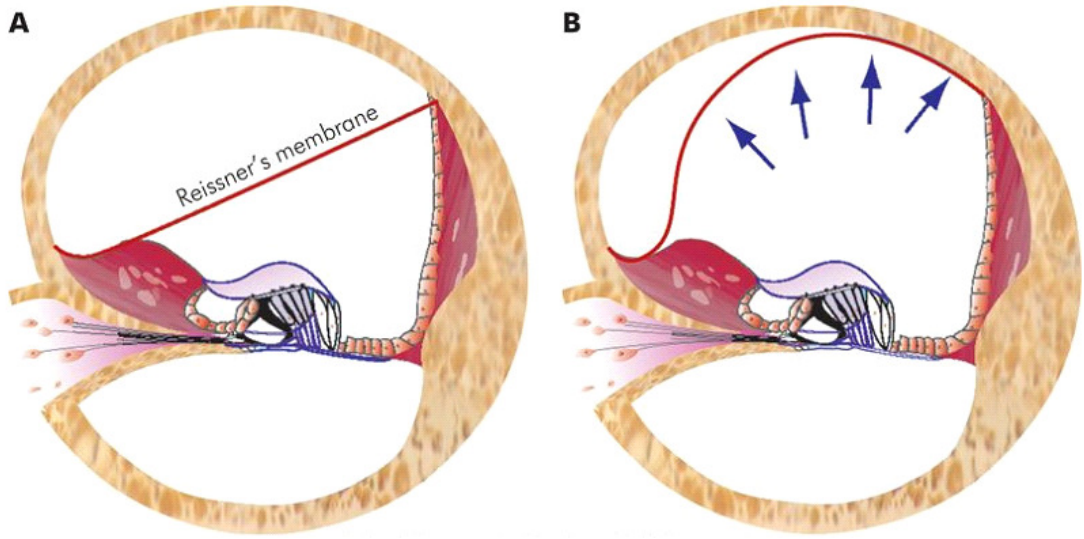


Fig. 5.1: (A) Normal cochlear duct. (B) Cochlear duct is distended with endolymph pushing the Reissner's membrane into scala vestibuli.

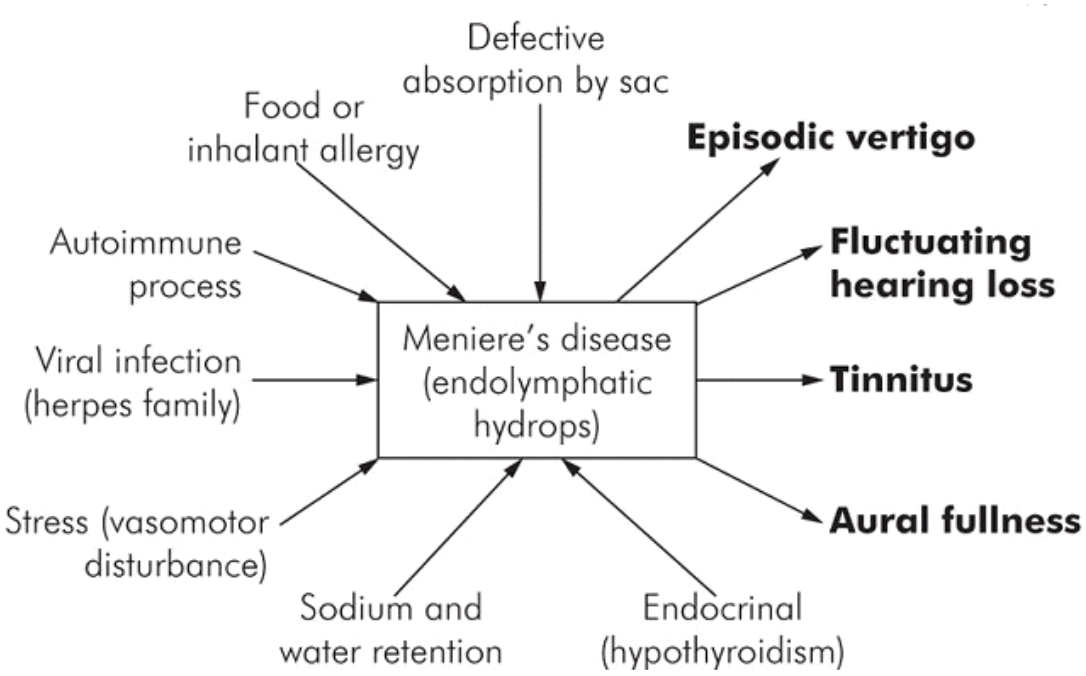
The main pathology is distension of endolymphatic system, mainly affecting the cochlear duct (scala media) and the saccule, and to a lesser extent the utricle and semicircular canals. The dilatation of cochlear duct is such that, it may completely fill the scala vestibuli; there is marked bulging of Reissner's membrane which may even herniate through the helicotrema

into the apical part of scala tympani. The distended saccule may come to lie against the stapes footplate. The utricle and saccule may show out-pouchings into the semicircular canals

Aetiology

The main pathology in Meniere's disease is distension of endolymphatic system due to increased volume of endolymph. This can result either from increased production of endolymph or its faulty absorption or both. Normally, endolymph is secreted by stria vascularis, fills the membranous labyrinth and is absorbed through the endolymphatic sac.

The exact cause of Meniere's disease is not yet known. Various theories have been postulated.



1. Defective absorption by endolymphatic sac

Normally, endolymph is carried by the endolymphatic duct to the sac where it is absorbed. Defective absorption by the sac may be responsible for raised endolymph pressure. Experimental obstruction of endolymphatic sac and its duct also produces hydrops. Ischaemia of sac has been observed in cases of Meniere's disease undergoing sac surgery, indicating

poor vascularity and thus poor absorption by the sac. Distension of membranous labyrinth leads to rupture of Reissner's membrane and thus mixing of perilymph with endolymph, which is thought to bring about an attack of vertigo.

2. Vasomotor disturbance

There is sympathetic over-activity resulting in spasm of internal auditory artery and/or its branches, thus interfering with the function of cochlear or vestibular sensory neuroepithelium. This is responsible for deafness and vertigo. Anoxia of capillaries of stria vascularis also causes increased permeability, with transudation of fluid and increased production of endolymph.

3. Allergy

The offending allergen may be a foodstuff or an inhalant. In these cases, inner ear acts as the "shock organ" producing excess of endolymph. Nearly 50% of patients with Meniere's disease have concomitant inhalant and/or food allergy.

It is possible that Meniere's disease is multifactorial, resulting in the common end point of endolymphatic hydrops with classical presentation.

4. Sodium and water retention

Excessive amounts of fluid are retained leading to endolymphatic hydrops.

5. Hypothyroidism

About 3% of cases of Meniere's disease are due to hypothyroidism. Such cases benefit from thyroid replacement therapy.

6. Autoimmune and viral aetiologies

Have also been suggested on the basis of experimental, laboratory and clinical observations.

Treatment of Menière's disease

Medical treatment with vasodilatory drugs such as betahistine may be useful. Nicotinic acid in a dose sufficient to cause flushing is an alternative. Menière's disease might be associated with electrolyte imbalance, and so a salt-restricted diet combined with a diuretic is often recommended

2. Benign paroxysmal positional vertigo (BPPV)

Peripheral (Lesions of end organs vestibular nerve)	**Central (Lesions of brainstem and central connections)**
• Meniere's disease • Benign paroxysmal positional vertigo • Vestibular neuronitis • Labyrinthitis • Vestibulotoxic drugs • Head trauma • Perilymph fistula • Syphilis • Acoustic neuroma	• Vertebrobasilar insufficiency • Posterior inferior cerebellar artery syndrome • Basilar migraine • Cerebellar disease • Multiple sclerosis • Tumours of brainstem and fourth ventricle • Epilepsy • Cervical vertigo

It has been demonstrated that otoconial debris, consisting of crystals of calcium carbonate, is released from the degenerating macula of the utricle and floats freely in the endolymph. When it settles on the cupula of posterior semicircular canal in a critical head position, it causes displacement of the cupula and vertigo. The vertigo is fatiguable on assuming the same position repeatedly due to dispersal of the otoconia but can be induced again after a period of rest. Thus, typical history and Hallpike manoeuvre establishes the diagnosis.

It is characterised by vertigo when the head is placed in a certain critical position. There is no hearing loss or other neurologic symptoms. Positional testing establishes the diagnosis and helps to differentiate it from positional vertigo of central origin. Disease is caused by a disorder of posterior semicircular canal though many patients have history of head trauma and ear infection.

The condition can be treated by performing Epley's manoeuvre**.** The principle of this manoeuvre is to reposition the otoconial debris from the posterior semicircular canal back into the utricle. The doctor stands behind the patient and the assistant on the side. The patient is made to sit on the table so that when he is made to lie down, his head is beyond the edge of the table as is done in Dix-Hallpike manoeuvre. His face is turned 45° to the affected side.

There should be a pause at each position till there is no nystagmus or there is slowing of nystagmus, before changing to the next position. After manoeuvre is complete, patient should maintain an upright posture for 48 hours. Eighty percent of the patients will be cured by a single manoeuvre. If the patient remains symptomatic, the manoeuvre can be repeated. A bone vibrator placed on the mastoid bone helps to loosen the debris.

3. Vestibular neuronitis

It is characterized by severe vertigo of sudden onset with no cochlear symptoms. Attacks may last from a few days to 2 or 3 weeks. It is thought to occur due to a virus that attacks vestibular ganglion. Management of acute attack is similar to that in Meniere's disease. The disease is usually self-limiting.

4. Labyrinthitis

Circumscribed labyrinthitis is seen in cases of unsafe type of CSOM, and fistula test is positive.

Serous labyrinthitis is caused by trauma or infection (viral or bacterial) adjacent to inner ear but without actual invasion. There is severe vertigo and sensorineural hearing loss. A partial or full recovery of inner ear functions is possible if treated early.

Purulent labyrinthitis is a complication of CSOM. There is actual bacterial invasion of inner ear with total loss of cochlear and vestibular functions. Vertigo in this condition is due to acute vestibular failure. There is severe nausea and vomiting. Nystagmus is seen to the opposite side due to destruction of the affected labyrinth.

5. Vestibulotoxic drugs

Several drugs cause ototoxicity by damaging the hair cells of the inner ear. Some primarily affect the cochlear while others affect the vestibular labyrinth. Aminoglycoside antibiotics particularly streptomycin, gentamicin, kanamycin have been shown to affect hair cells of the crista ampullaris and to some extent those of the maculae. Certain other drugs which cause dizziness or unsteadiness are antihypertensives, labyrinthine sedatives, oestrogen preparations, diuretics, antimicrobials (nalidixic acid, metronidazole) and antimalarials. However, their mode of action may be different.

6. Head trauma

Head injury may cause concussion of labyrinth, completely disrupt the bony labyrinth or VIIIth nerve, or cause a perilymph fistula. Severe acoustic trauma, such as that caused by an explosion can also disturb the vestibular end organ (otoliths) and result in vertigo.

7. Perilymph fistula

In this condition, perilymph leaks into the middle ear through the oval or round window. It can follow as a complication of stapedectomy, or ear surgery when stapes is accidentally dislocated. It can also result from sudden pressure changes in the middle ear (e.g. barotrauma, diving, forceful Valsalva) or raised intracranial pressure (weightlifting or vigorous coughing). A perilymph fistula causes intermittent vertigo and fluctuating sensorineural hearing loss, sometimes with tinnitus and sense of fullness in the ear.

8. Syphilis

Syphilis of inner ear, both acquired and congenital, causes dizziness in addition to sensorineural hearing loss. Late congenital syphilis usually manifesting between 8 and 20 years, mimics Meniere's disease with episodes of acute vertigo, sensorineural hearing loss and tinnitus. Hennebert's sign, i.e. a positive fistula test in the presence of an intact tympanic membrane, is present in congenital syphilis. Neurosyphilis (tertiary acquired) can cause

central type of vestibular dysfunction.

9. Acoustic neuroma

It has been classified in peripheral vestibular disorders as it arises from CN VIII within internal acoustic meatus. It causes only unsteadiness or vague sensation of motion. Severe episodic vertigo, as seen in the end organ disease, is usually missing.

Other tumours of temporal bone (e.g. glomus tumour, carcinoma of external or middle ear and secondaries), destroy the labyrinth directly and cause vertigo[41].

Duration of vertigo

• Menière's disease – hours.

• Benign paroxysmal positional vertigo – seconds only.

• Sudden vestibular failure – days

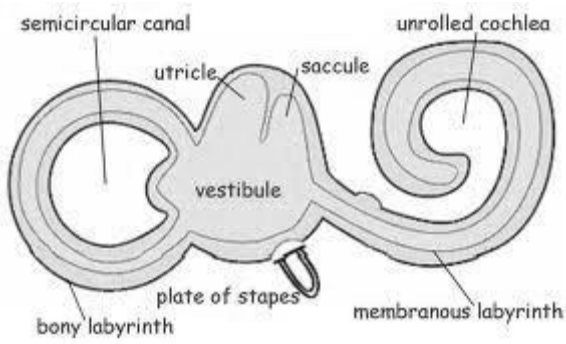
Operation is advised if the symptoms are not controlled by medication. Conservative surgical procedures aim to protect hearing, and include decompression of the endolymphatic sac and selective division of the vestibular branch of the vestibulocochlear nerve (vestibular neurectomy). Labyrinthectomy, with total destruction of the membranous labyrinth, guarantees relief from the vertigo but at the expense of total loss of hearing in that ear. This is often acceptable if the hearing remains only as a painful distorted shred in the affected ear when the other is normal.

Symptomatic treatment of vertigo

Symptoms may be relieved by sedatives such as prochlorperazine, cinnarizine and other antihistamines. Diazepam is also useful. In a severe attack, bed rest will be necessary whatever the cause. Drugs may be given intramuscularly or as suppositories. Once the acute stage is over, sedatives are continued in small doses for several weeks or months.

If vestibular deficit, rather than irritation of a labyrinthine system, is pronounced, vestibular sedatives may exacerbate the symptoms.

This often happens in the degenerative changes of old age and in bilateral Menière's disease, or ototoxic damage. Patients can be helped by graded head and eye movement exercises, designed to accelerate the process of central compensation. These head exercises should be taught and supervised by specially trained physiotherapists. Other treatment is directed at identified causes, including surgical exploration of any middle ear in which cholesteatomatous erosion of the middle ear is suspected.[41,42]

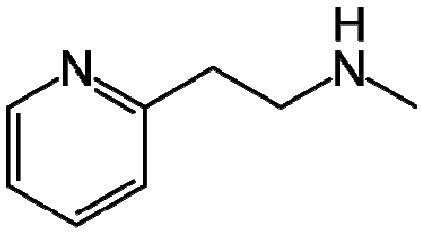


6. DRUG PROFILE

DRUG PROFILE

BETAHISTINE HYDROCHLORIDE[46-48]

Chemical structure[46]



.2HCl

Chemical name[46]

Methyl[2-(pyridin-2-yl)ethyl]amine dihydrochloride.

CAS number[46]

5579-84-0

Molecular formula[46]

$C_8H_{12}N_2.2HCl$

Molecular weight[46]

209.11

Description[48]

A white to off white, crystalline powder; sometimes clumped, odourless or almost odourless, very hygroscopic.

Solubility[48]

Very soluble in water, soluble in ethanol (95%), practically insoluble in 2-Propanol.

Melting point

150-154 °C

Category

Anti-histaminic

Pharmacology[47]

Pharmacokinetics

Absorption :

When given orally, betahistine is rapidly absorbed from the gastrointestinal tract.

Protein binding :

5%

Half-life :

3-4 hours

Metabolism & elimination:

Metabolized by liver and excreted through urine (85-90%)

Mechanism of action[47]

Betahistine has a very strong affinity as an antagonist for histamine H_3 receptors and a weak affinity as an agonist for histamine H_1 receptors. Betahistine seems to dilate the blood vessels within the inner ear which can relieve pressure from excess fluid and act on the smooth muscle.

Indications[47]

Reduction of episodes of vertigo association with Ménière's disease.

Dosage[46]

Adult : 16mg tds

Maintenance : 24-48 mg daily

Adverse effects[46]

- Headache.
- Low level of gastric side effects.
- Insomnia
- Nausea can be a side effect, but the patient is generally already experiencing nausea due to the vertigo so it goes largely unnoticed.

Contraindications[46]

Betahistine should not be given to neonates, children, during pregnancy and lactation and in patients with pheochromocytoma. It should be used with caution in patients with asthma or peptic ulcer.

Drug interactions[47]

Alcohol

Storage[47]

Store in a well closed container, at room temperature, below 30^{o} C.

7. EXCIPIENTS PROFILE

EXCIPIENTS PROFILE:

HYPROMELLOSE[49]

Nonproprietary Names

BP: Hypromellose

JP: Hypromellose

PhEur: Hypromellose

USP: Hypromellose

Synonyms

Benecel MHPC ; E464; hydroxypropyl methylcellulose; HPMC;hypromellosum; Methocel ; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose; MHPC; Pharmacoat; Tylopur; Tylose MO

Chemical Name and CAS Registry Number

Cellulose hydroxypropyl methyl ether [9004-65-3]

Description

Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder.

Functional Category

Bio adhesive material; coating agent; controlled-release agent; dispersing agent; dissolution enhancer; emulsifying agent; emulsion stabilizer; extended-release agent; film-forming agent; foaming agent; granulation aid; modified-release agent; mucoadhesive; release-modifying agent; solubilizing agent; stabilizing agent; suspending agent; sustained-release agent; tablet binder; thickening agent; viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology

In oral products, hypromellose is primarily used as a tablet binder, in film-coating, and as a matrix for use in extended-release tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Hypromellose is also used in liquid oral dosage forms as a suspending and/or thickening agent at concentrations ranging from 0.25–5.0%. Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets. Lower-viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents. Hypromellose is used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments.

Incompatibilities

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

Safety

Hypromellose is generally regarded as a nontoxic and non-irritating material, although excessive oral consumption may have a laxative effect.

LD50(mouse, IP): 5 g/kg

LD50(rat, IP): 5.2 g/kg

Handling Precautions

Hypromellose dust may be irritating to the eyes, so eye protection is recommended. Excessive dust generation should be avoided to minimize the risks of explosion. Hypromellose is combustible.

MICROCRYSTALLINE CELLULOSE[49]

Nonproprietary Names

BP: Microcrystalline Cellulose

JP: Microcrystalline Cellulose

PhEur: Cellulose, Microcrystalline

USP-NF: Microcrystalline Cellulose

Synonyms

Avicel PH; Cellets ; Celex; cellulose gel; hellulosum microcristalli-num; Celphere ; Ceolus KG ; crystalline cellulose; E460; Emcocel; Ethispheres ; Fibrocel; MCC Sanaq; Pharmacel; Tabulose ; Vivapur.

Chemical Name and CAS Registry Number

Cellulose [9004-34-6]

Empirical Formula and Molecular Weight

$(C_6H_{10}O_5)_n$ 36 000

where n 220.

Functional Category

Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.

Description

Microcrystalline cellulose is a white, odorless, tasteless, crystalline powder composed of porous particles.

Use	Concentration(%)
Adsorbent	20-90
Antiadherent	5-20
Capsule binder/diluent	20-90
Tablet disintegrant	5-15
Tablet binder/diluent	20-90

Stability and Storage Conditions

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

Incompatibilities

Microcrystalline cellulose is incompatible with strong oxidizing agents.

Safety

Microcrystalline cellulose is not absorbed systemically following oral administration and thus has little toxic potential. Consumption of large quantities of cellulose may have a laxative effect. Deliberate abuse of formulations containing cellulose, either by inhalation or by injection, has resulted in the formation of cellulose granulomas.

Handling Precautions

Microcrystalline cellulose may be irritant to the eyes. Gloves, eye protection, and a dust mask are recommended. In the UK, the workplace exposure limits for cellulose have been set at 10 mg/m^3 long-term (8-hour TWA) for total inhalable dust and 4 mg/m^3 for respirable dust; the short-term limit for total inhalable dust has been set at 20 mg/m^3.

SODIUM BICARBONATE[49]

Nonproprietary Names

BP: Sodium bicarbonate

JP: Sodium bicarbonate

PhEur: Natrii hydrogenocarbonas

USP: Sodium bicarbonate

Synonyms

Baking soda; E500; Effer-Soda; monosodium carbonate; Sal de Vichy; sodium acid carbonate; sodium hydrogen carbonate.

Chemical Name and CAS Registry Number

Carbonic acid monosodium salt [144-55-8]

Empirical Formula and Molecular Weight

$NaHCO_3$-84.01

Functional Category

Alkalizing agent

Applications in Pharmaceutical Formulation or Technology

Sodium bicarbonate is generally used in pharmaceutical formulations as a source of carbon dioxide in effervescent tablets and granules. It is also widely used to produce or maintain an alkaline pH in a preparation.

Use	Concentration (%)
Buffer in tablets	10-40
effervescence	25-50
Isotonic injection/infusion	1.39

Description

Sodium bicarbonate occurs as an odorless, white, crystalline powder with a saline, slightly alkaline taste.

Incompatibilities

Sodium bicarbonate intensifies the darkening of salicylates. In solution, sodium bicarbonate has been reported to be incompatible with many drug substances such as ciprofloxacin, amiodarone, nicardipine, and levofloxacin.

Safety

Sodium bicarbonate is metabolized to the sodium cation, which is eliminated from the body by renal excretion, and the bicarbonate anion, which becomes part of the body's bicarbonate store. Any carbon dioxide formed is eliminated via the lungs. Administration of excessive amounts of sodium bicarbonate may thus disturb the body's electrolyte balance, leading to metabolic alkalosis or possibly sodium overload with potentially serious consequences.

LD50 (mouse, oral): 3.36 g/kg

LD 50 (rat, oral): 4.22 g/kg

Handling Precautions

Eye protection and gloves are recommended.

POVIDONE K30[49]

Nonproprietary Names

BP: Povidone

JP: Povidone

PhEur: Povidonum

USP: Povidone

Synonyms

E1201;Kollidon ; Plasdone ; poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; polyvinylpyrrolidone; PVP; 1-vinyl-2-pyrrolidinone polymer.

Chemical Name and CAS Registry Number

1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

Empirical Formula and Molecular Weight

$(C_6 H_9NO)_n$ 2500–3 000 000

Approximate molecular weight for different grades of povidone.

K-value	Approximate molecular weight
12	2 500
15	8 000
17	10 000
25	30 000
30	50 000

60	400 000
90	1 000 000
120	3 000 000

Functional Category

Disintegrant; dissolution aid; suspending agent; tablet binder.

Applications in Pharmaceutical Formulation or Technology

In tableting, povidone solutions are used as binders in wet granulation processes. Povidone is also added to powder blends in the dry form and granulated in situ by the addition of water, alcohol, or hydroalcoholic solutions. Povidone is used as a solubilizer in oral and parenteral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms. Povidone solutions may also be used as coating agents

Uses of povidone.

Use	Concentration (%)
Carrier for drugs	10–25
Dispersing agent	Up to 5
Eye drops	2–10
Suspending agent	Up to 5
Tablet binder, tablet diluent, or coating agent	0.5-5

Description

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder.

Stability and Storage Conditions

Aqueous solutions are susceptible to mold growth and consequently require the addition of suitable preservatives. Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.

Incompatibilities

It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin, and other compounds; The efficacy of some preservatives, e.g. thiomersal, may be adversely affected by the formation of complexes with povidone.

Safety

Povidone may be regarded as essentially nontoxic since it is not absorbed from the gastrointestinal tract or mucous membranes. Povidone additionally has no irritant effect on the skin and causes no sensitization. Reports of adverse reactions to povidone primarily concern the formation of subcutaneous granulomas at the injection site of intramuscular injections formulated with povidone. A temporary acceptable daily intake for povidone has been set by the WHO at up to 25 mg/kg body-weight.

LD50 (mouse, IP): 12 g/kg

Handling Precautions

Eye protection, gloves, and a dust mask are recommended.

ISOPROPYL ALCOHOL[49]

Nonproprietary Names

BP: Isopropyl alcohol

JP: Isopropanol

PhEur: Alcohol isopropylicus

USP: Isopropyl alcohol

Synonyms

Dimethyl carbinol; IPA; isopropanol; petrohol; 2-propanol; sec- propyl alcohol.

Chemical Name and CAS Registry Number

Propan-2-ol [67-63-0]

Empirical Formula and Molecular Weight

$C_3 H_8O$ - 60.1

Functional Category

Disinfectant; solvent.

Applications in Pharmaceutical Formulation or Technology

Isopropyl alcohol (propan-2-ol) is used in cosmetics and pharmaceutical formulations primarily as a solvent in topical formulations. Although it is used in lotions, the marked degreasing properties of isopropyl alcohol may limit its usefulness in preparations used repeatedly. Isopropyl alcohol is also used as a solvent both for tablet film-coating and for tablet granulation, where the isopropyl alcohol is subsequently removed by evaporation. It has also been shown to significantly increase the skin permeability of nimesulide from carbomer 934. Isopropyl alcohol has some antimicrobial activity and a 70% v/v aqueous solution is used as a topical disinfectant.

Description

Isopropyl alcohol is a clear, colorless, mobile, volatile, flammable liquid with a characteristic, spirituous odor resembling that of a mixture of ethanol and acetone; it has a slightly bitter taste.

Solubility:

Miscible with benzene, chloroform, ethanol (95%), ether, glycerin, and water. Soluble in acetone; insoluble in salt solutions. Forms an azeotrope with water, containing 87.4% w/w isopropyl alcohol (boiling point 80.37 8 C).

Stability and Storage Conditions

Isopropyl alcohol should be stored in an airtight container in a cool, dry place.

Incompatibilities

Incompatible with oxidizing agents such as hydrogen peroxide and nitric acid, which cause decomposition. Isopropyl alcohol may be salted out from aqueous mixtures by the addition of sodium chloride, sodium sulfate, and other salts, or by the addition of sodium hydroxide.

Safety

It is readily absorbed from the gastrointestinal tract and may be slowly absorbed through intact skin. Prolonged direct exposure of isopropyl alcohol to the skin may result in cardiac and neurological deficits. In neonates, isopropyl alcohol has been reported to cause chemical burns following topical application. Isopropyl alcohol is metabolized more slowly than ethanol, primarily to acetone. The lethal oral dose is estimated to be about 120–250 mL although toxic symptoms may be produced by 20 mL.

Handling Precautions

Isopropyl alcohol may be irritant to the skin, eyes, and mucous membranes upon inhalation. Eye protection and gloves are recommended. Isopropyl alcohol should be handled in a well-ventilated environment.

8. MATERIALS AND METHODS

MATERIALS AND METHODS

The list of drug and excipients, their manufacturers and use in the present study are shown in Table 8.1

Tab. 8.1: List of materials and their applications in formulation

S.No	Name of material	Manufacturer / supplier	Use in formulation
1	Betahistine hydrochloride	Madras Pharmaceutical (P) Ltd	Active ingredient
2	HPMC K4M	Shandong Head Co., Ltd	Hydrophilic polymer
3	HPMC K100M	Shandong Head Co., Ltd	Hydrophilic polymer
4	Micro crystalline cellulose	Amit cellulose	Diluent
5	Sodium bicarbonate	Indian research products	Gas generating agent
6	PVP K30	Jiao Zuo yuanhai fine Chemicals Ltd.,	Binding agent
7	Magnesium stearate	Zudila enterprise	Lubricant
8	Isopropyl alcohol	Microfine chemicals	Solvent

The list of instruments/equipments used in the present study and their manufacturer are shown in Table 8.2

Tab. 8.2: List of equipment used

S.NO	Equipment / instruments	Manufacturer /supplier
1	Electronic weighing balance	Shimadzu, Japan
2	Hot air oven	MC Dalal, Chennai
3	10 Station compression machine	Rimek, India
4	Vernier caliper	Mitutoyo, Japan
5	Monsanto hardness tester	Erweka, Mumbai
6	Friabilator	Electrolab, India
7	Dissolution tester	Veego, India
8	UV-visible spectrophotometer	Shimadzu, Japan
9	Fourier transform infrared spectrophotometer	Nicolet, India

METHODOLOGY

Preformulation studies

The Preformulation studies are conducted to establish the physiochemical characteristics of the drug and its compatibility with the various excipients. The Preformulation studies are necessary to formulate drug into stable, safe and effective dosage form.

Drug-excipient compatibility study

The drug and excipients selected for the formulation are evaluated for physical and chemical compatibility studies.

Physical compatibility study

The physical compatibility studies are conducted to provide valuable information to the formulator in selecting the appropriate excipients for the formulation. It was done by mixing the drug and excipients and kept at room temperature and at 40°C and 75%RH. Any color change of the physical mixture was observed visually.[50]

Chemical compatibility study

Pure drug, polymers, excipients and drug-excipient mixture were subjected to FTIR to investigate the drug-excipient interactions. The IR spectra of test samples were obtained using potassium bromide pellet method.[51]

Preparation of 0.1 N HCl

8.5 mL of hydrochloric acid was mixed with about 600 ml of distilled water and the volume was made up to 1000 ml with distilled water.[52]

Calibration curve

100mg of BET hydrochloride was weighed and transferred into 100 mL standard flask and made up to 100 ml with 0.1 N HCl. From the above solution 10 mL was taken and made up to 100 mL using 0.1N HCL. From the above solution 2 mL, 4 mL, 6 mL, 8 mL and 10 mL

were taken and made up to 100mL using 0.1N HCL. The absorbance of the resulting solutions was measured at 261 nm[53] using UV spectrophotometer. Calibration curve was plotted taking concentration on X axis and absorbance on Y axis.

Pre formulation studies of the blends[54]

The flow property measurements include bulk density, tapped density, angle of repose, compressibility index and Hausner's ratio. The flow property measurements of drugs and blends are determined.

I. Bulk density

Bulk density is the ratio of weight of powder to bulk volume. A sample of 10g of powder was carefully introduced into measuring cylinder with the aid of funnel and volume occupied by the powder was noted. Bulk density is expressed in g/ml.

$$\text{Bulk density} = \frac{M}{V_b}$$

Where,

M = weight of sample in grams

Vb=bulk volume

II. Tapped density

Tapped density is the ratio of weight of powder to tapped volume of powder. The 10g of powder was introduced into the measuring cylinder with the aid of funnel and tapped from the height of 1 inch for 500 times on a hard wooden surface at 2 seconds interval and the volume obtained was noted. Tapped density is expressed in g/ml.

$$\text{Tapped density} = \frac{M}{Vt}$$

Where,

M = weight of sample in grams

Vt= tapped volume

III. Angle of repose

Angle of repose measures the frictional force involved in the powder. It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane. It is determined by fixed funnel method. The powder mixture allowed to flow through the funnel fixed to a stand at define height. The angle of repose is then calculated by the formula

$$\theta = \tan^{-1}(h/r)$$

where,

θ= angle of repose in degrees

h= height of the pile of powder in cm

r= radius of pile of powder in cm

Tab. 8.3: Values of angle of repose, compressibility index, Hausner's ratio

Flow property	**Angle of repose (in degrees)**	**Compressibility index (%)**	**Hausner's ratio**
Excellent	25-30	<10	1.00-1.11
Good	31-35	11-15	1.12-1.18
Fair	36-40	16-20	1.19-1.25
Passable	41-45	21-25	1.26-1.34
Poor	46-55	26-31	1.35-1.45
Very poor	56-65	32-37	1.46-1.59
Very very poor	>65	>38	>1.60

IV. Compressibility index or Carr's index

Compressibility index is the measure of flow property of a powder. It is measured for determining the relative importance of inter particulate interactions. It is expressed in percentage and calculated by formula mentioned below.

$$\text{Compressibility index} = \left(\frac{\text{Tapped density - bulk density}}{\text{Tapped density}} \right) \times 100$$

V. Hausner's ratio

Hausner's ratio is the measure of propensity of powder to be compressed and also inter particulate interactions. Hausner's ratio is calculated by the formula mentioned below.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Formulation of sustained release BET hydrochloride floating tablets

The sustained release tablets of BET hydrochloride were prepared by wet granulation technique. Different grades of HPMC polymer such as HPMC K4M and HPMC K100M were used alone and in different ratios. All the ingredients except magnesium stearate were sieved through mesh no. 22 and transferred to a clean porcelain mortar. PVP (5% w/w) binding solution was added to the powder mixture in small quantities, while mixing thoroughly after each addition until a coherent mass was formed. Then it was passed through sieve no.10 and the wet granules were dried in hot air oven at 60^{o}C for 30 min. The dried granules were lubricated with magnesium stearate and compressed into tablet using 10 station tablet compression machine.

Tab. 8.4: Formulation of Floating tablets

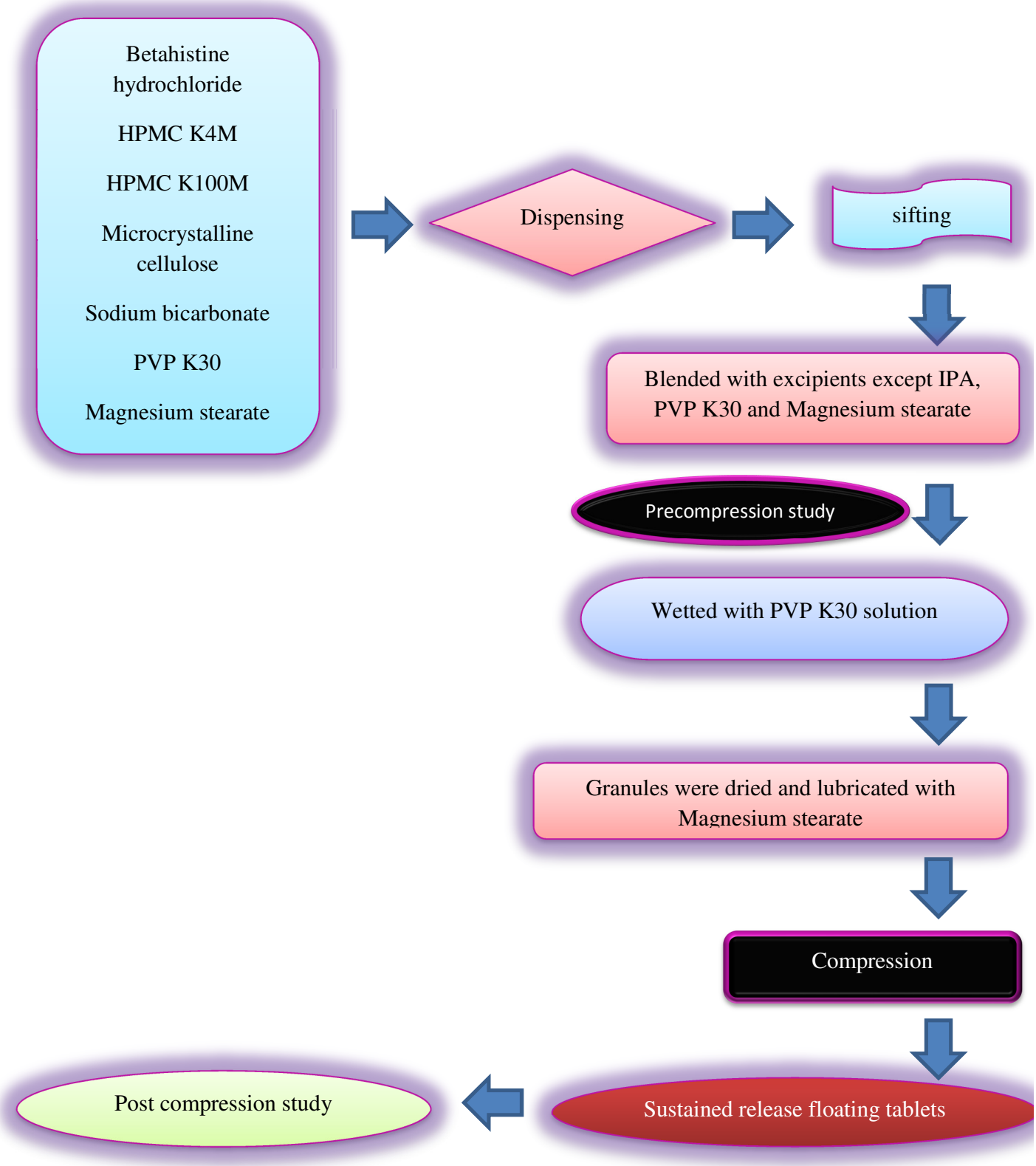
Ingredients	F-I	F-II	F-III	F-IV	F-V	F-VI	F-VII	F-VIII	F-IX
Betahistine hydrochloride	24	24	24	24	24	24	24	24	24
HPMC K4M	120	150	180	-	-	-	30	60	90
HPMCK100M	-	-	-	120	150	180	90	90	90
Microcrystalline cellulose	85	55	25	85	55	25	85	55	25
Sodium bicarbonate	50	50	50	50	50	50	50	50	50
PVP K30	15	15	15	15	15	15	15	15	15
Magnesium stearate	6	6	6	6	6	6	6	6	6
Isopropyl alcohol	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06

Average weight of one tablet = 300 mg

Tab. 8.5: % of polymers used in formulation of BET hydrochloride floating tablets

Formulation	% of Polymer used	
	HPMC K4M	HPMC K100M
F-I	40	-
F-II	50	-
F-III	60	-
F-IV	-	40
F-V	-	50
F-VI	-	60
F-VII	10	30
F-VIII	20	30
F-IX	30	30

Fig.8.1: Schematic representation of formulation development of BET hydrochloride floating tablets



Evaluation of Tablets:

Description:[55]

Ten tablets were selected randomly and placed in a petridish. The tablets were observed from both the sides for colour, shape and appearance.

Uniformity of Weight: [56]

Twenty tablets were selected at random from each batch. The individual tablet was weighed and the average weight was determined. The individual weight was compared with the average weight. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the table 8.6 and none deviates by more than twice that percentage.

Tab. 8.6: Uniformity of Weight

S.No	Average weight of a tablet	% Deviation
1.	80 mg or less	10
2.	More than 80 mg but less than 250 mg	7.5
3.	250 mg or more	5

Diameter and thickness: [57]

Diameter and thickness of tablets were determined using vernier Caliper. Five tablets from each batch were used and average value was calculated.

Hardness: [57]

The crushing strength of the tablets were measured using a Monsanto Hardness tester. Five tablets from each batch were tested randomly and the average was recorded.

Friability: [58]

Tablets of weight equivalent to 6.5 g were weighed and placed in a Roche Friabilator. The equipment was rotated at a speed of 25 rpm for 4 minutes. The tablets were taken out, dedusted and reweighed. The percentage friability of the tablets was measured as per the following formula:

$$F = (1-W/W_0) \text{ X } 100$$

Where

W is the weight of the tablets after the test

W_0 is the weight of the tablets before the test

Drug Content: [57]

10 tablets were weighed and powdered. The average weight was determined. The powder equivalent to 24 mg of drug was weighed and transferred to a 100 mL volumetric flask. It was then made up to volume with 0.1 N HCl. 10 mL was pipetted out into a 100 ml standard flask and made up to volume with 0.1 N HCl. The absorbance of the resulting solution was measured at 261 nm using UV-Visible Spectrophotometer taking 0.1 N HCl as blank. The content of BET hydrochloride was then calculated.

***In vitro* floating studies:**[57]

Floating time was determined using USP dissolution apparatus-II, 900 mL of 0.1N HCl and temperature was maintained at 37 ± 0.5^0C. The duration of floating and floating lag time, were measured by visual observation.

Determination of Swelling Index:[57]

The swelling index of tablets was determined in 0.1N HCl (pH 1.2) at room temperature. The swollen weight of the tablet was determined at predefined time intervals

over a period of 24 h. The swelling index (SI), expressed as a percentage, was calculated from the following equation.

SI = Weight of tablet at time (t) - Initial weight of tablet/Initial weight of tablet

***In vitro* release study of the tablets:** [57]

In vitro dissolution studies were carried out using USP dissolution test apparatus-II, employing a paddle at 50 rpm using 900 mL of 0.1 N HCl at 37±0.5^{0}C as dissolution medium. One tablet was used in each test. At predetermined time intervals 10 mL of the samples were withdrawn by means of a pipette. The medium withdrawn at each interval was replaced with the same quantity of fresh dissolution medium. The samples were analyzed for drug release by measuring the absorbance at 261 nm using UV-Visible spectrophotometer. All the studies were conducted in triplicate.

RELEASE KINETICS OF THE OPTIMIZED FORMULATION:[59]

To study the kinetics, data obtained from *in vitro* release were plotted in various kinetics models.

1. Zero order release model:

Zero order models describe the systems where the drug release rate is independent of its concentration.

$$\mathbf{C = K_0\, t}$$

Where

C – Cumulative percentage of drug released

K_0 - Zero-order constant

t – Time

A plot of time on x-axis and cumulative percentage of drug released on y-axis gives a straight line with slope (k_0) if it follows zero order kinetics.

2. First order release model:

First order models describe the systems where the release rate is dependent on the concentration.

$$\textbf{Log C = log } C_0 \textbf{ - K t/2.303}$$

Where

C – Cumulative percentage of drug remaining

C_0 - Initial concentration of drug

k – First order constant

A plot of time on x-axis and log cumulative percentage of drug remaining on y-axis gives a straight line with slope (k/2.303) if it follows first order kinetics.

3. Higuchi release model:

The Higuchi model describes the release from systems where the solid drug is dispersed in an insoluble matrix and the rate of release is related to the rate of drug diffusion.

$$\textbf{Q = kt}^{1/2}$$

Where

Q – Cumulative percentage of drug released

k – Constant reflecting the design variables of the system

t – Time

A plot of square root of time on x-axis and cumulative percentage drug released on y-axis gives a straight line if it follows Higuchi kinetics.

4. Hixson-Crowell release model:

The Hixson-Crowell cube root model describes the release from systems where there is a change in surface area and diameter of the tablets or particles.

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC}\, t$$

Where

Q_t – Cumulative percentage drug released in time t

Q_0 – initial amount of drug

K_{HC} – Rate constant for Hixson-Crowell rate equation

t – Time

A plot of time on x-axis and cube root of cumulative percentage of drug remaining on y-axis gives a straight line if it follows Hixson-Crowell kinetics.

5. Korsemeyer-Peppas model:

Korsemeyer-Peppas model derived a simple relationship which describes the drug release from a polymeric system.

$$M_t/M_\infty = Kt^n$$

Where

M_t/M_∞ - Fraction of drug released at time t

k – Release rate constant

n – Release exponent

A plot of log time on x-axis and log cumulative percentage of drug released on y-axis gives a straight line if it follows Korsemeyer-Peppas kinetics. The n value is used to characterize different release mechanism.

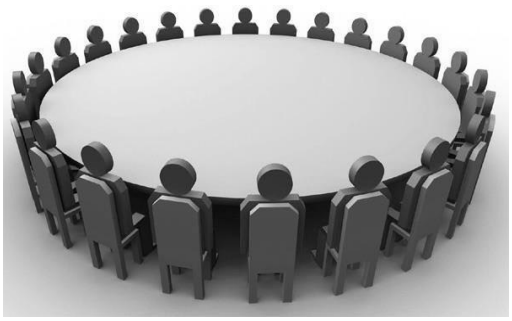
Tab. 8.7: Diffusion exponent and solute release mechanism for cylindrical shape

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45 < n <0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n > 0.89	Super case-II transport

In vitro drug release data were fitted to various models such as zero order, first order, Higuchi equation, Korsmeyer-Peppas equation, and Hixson-Crowell equation to know about the mechanism of drug release.

Stability studies

Short term stability studies were performed at a temperature of 40±2^{0}C and RH of 75±5% over a period of three months on the promising formulation. Sufficient number of tablets (20) were packed in amber colored screw capped bottles and kept in stability chamber maintained at 40±2^{0}C and RH 75±5%. Samples were taken at monthly intervals and tested for physical properties, drug content and *in vitro* drug release.



9. RESULTS AND DISCUSSION

RESULTS AND DISCUSSION

Physical compatibility study:

The drug and the excipients were tested for their physical compatibility in order to obtain a safe and efficient dosage form. The results of the compatibility study are listed in Table 9.1

Tab. 9.1: Physical Compatibility study of drug and excipients

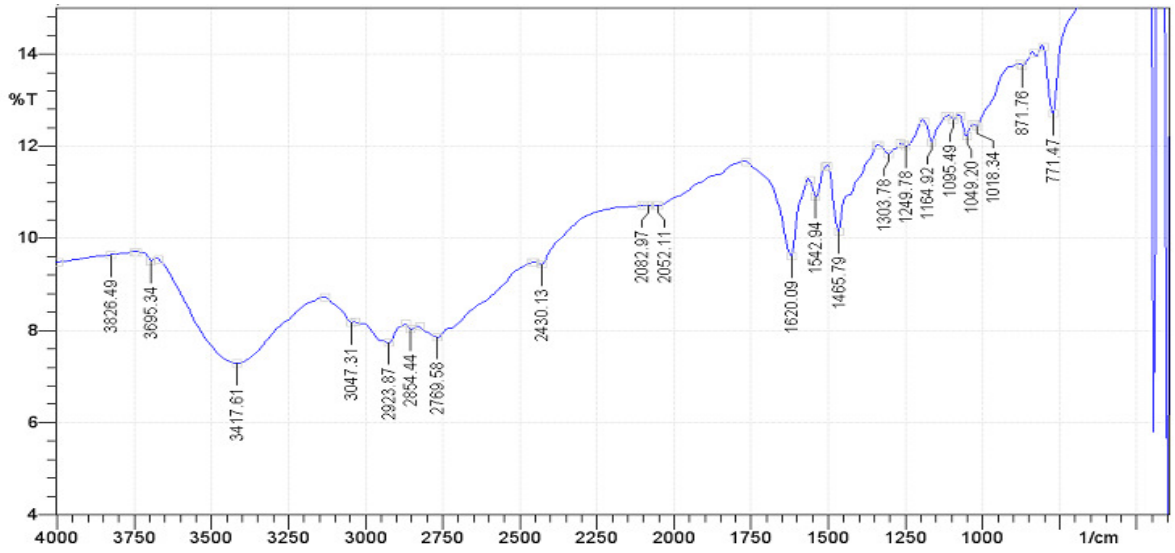
S.No	Drug and Excipients	Descriptions and conditions						
		Initial	Room temperature			40±2°C		
			days					
			10	20	30	10	20	30
1.	BET hydrochloride	Off-white coloured powder	NC	NC	NC	NC	NC	NC
2.	HPMC	White coloured powder	NC	NC	NC	NC	NC	NC
3.	BET+HPMC K4M	white coloured powder	NC	NC	NC	NC	NC	NC
4.	BET+HPMC K100M	White coloured powder	NC	NC	NC	NC	NC	NC
5.	BET + MCC	white coloured powder	NC	NC	NC	NC	NC	NC
6.	BET + Sodium bicarbonate	White coloured powder	NC	NC	NC	NC	NC	NC
7.	BET + PVP K 30	Pale yellow coloured powder	NC	NC	NC	NC	NC	NC
8.	BET + Magnesium stearate	White coloured powder	NC	NC	NC	NC	NC	NC

The physical compatibility study was performed and the results showed that there was no sign of incompatibility. The drug and the excipients are physically compatible.

FTIR Study – Identification and Compatibility of Drug and Polymer:

The identification of drug and the compatibility between the drug and polymers was carried out using FTIR. The FTIR spectra of the pure drug, drug polymer mixtures and tablet powder are shown in Figures 9.1 to 9.7 and interpretation are shown in table 9.2 to 9.8

Fig. 9.1: FTIR Spectrum of Betahistine hydrochloride



Tab. 9.2: FTIR Spectrum of BET HCl

Wave Number (cm^{-1})	Interpretation
3417	N-H Stretching
2923	C-H Stretching (aliphatic)
1620	C=C Stretching
1485	C-N Stretching

Fig. 9.2: FTIR Spectrum of BET hydrochloride and HPMC K4M

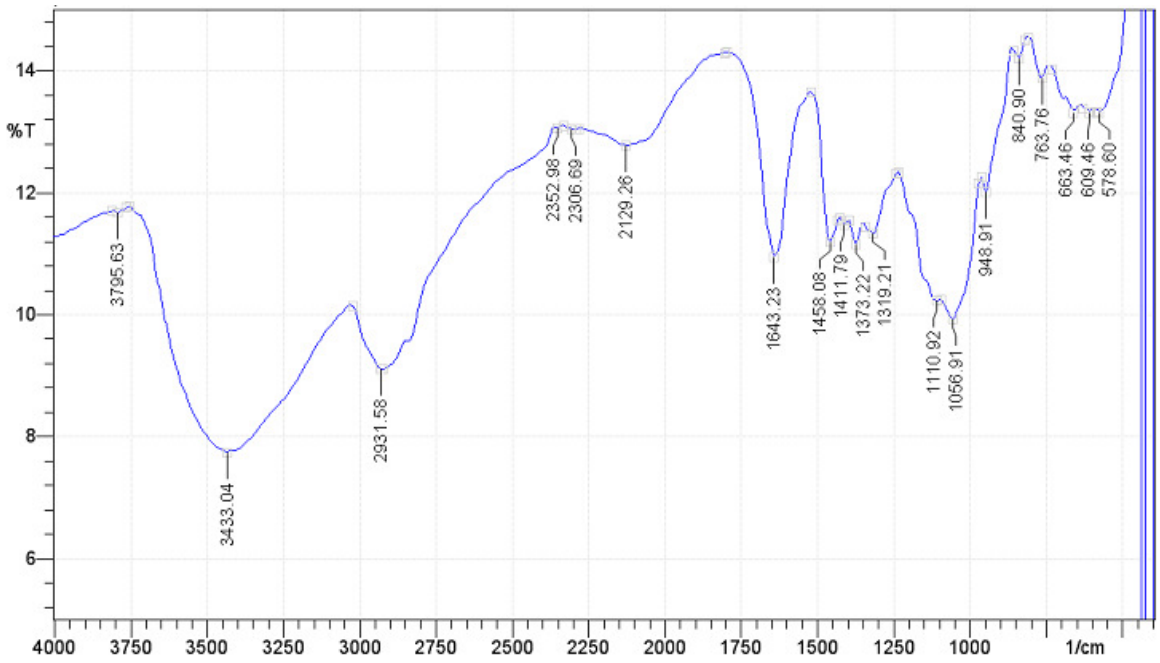
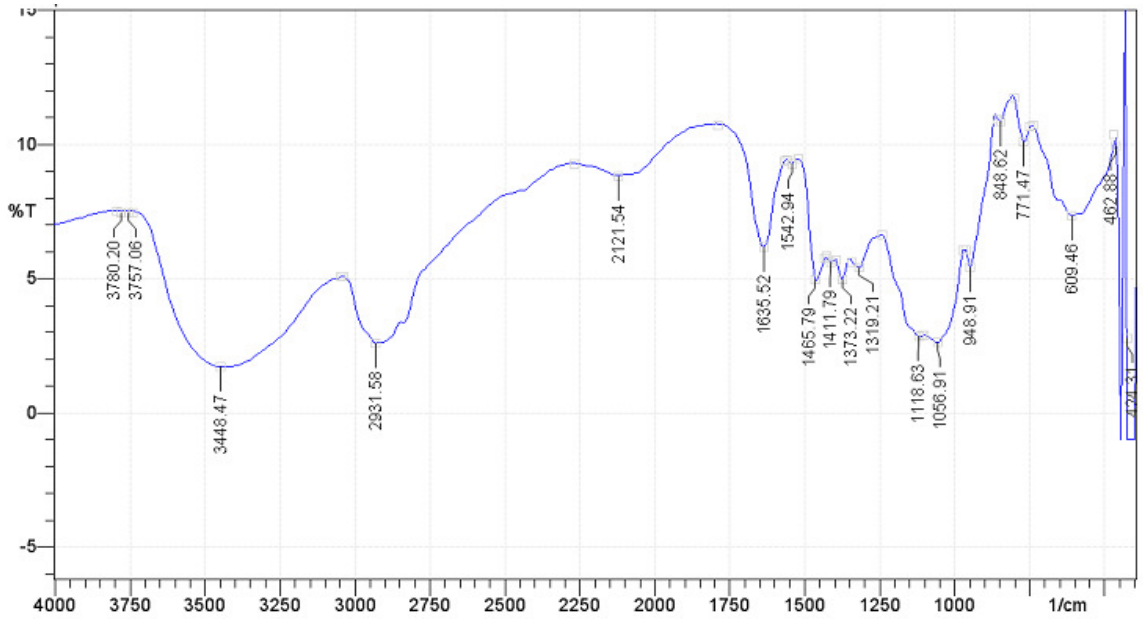


Table 9.3: FTIR Spectrum of BET HCl and HPMC K4M

Wave Number (cm^{-1})	Interpretation
3433	N-H Stretching
2931	C-H Stretching (aliphatic)
1643	C=C Stretching
1458	C-N Stretching

The peaks observed in the FTIR spectrum of BET HCl with HPMC K4M showed no shift and no disappearance of characteristic peaks of drug. This suggests that there is no interaction between the drug and HPMC K4M.

Fig. 9.3: FTIR Spectrum of BET HCl and HPMC K100M

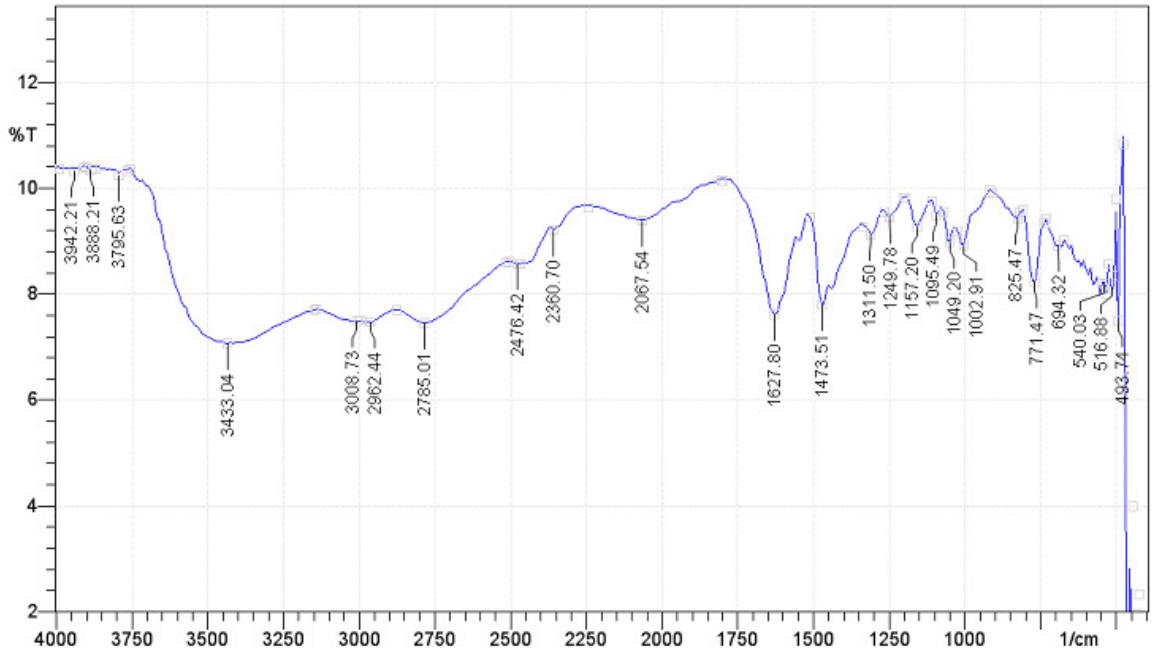


Tab. 9.4: FTIR Spectrum of BET HCl and HPMC K100M

Wave Number (cm^{-1})	Interpretation
3448	N-H Stretching
2931	C-H Stretching (aliphatic)
1635	C=C Stretching
1485	C-N Stretching

The peaks observed in the FTIR spectrum of BET HCl with HPMC K100M showed no shift and no disappearance of characteristic peaks of drug. This suggests that there is no interaction between the drug and HPMC K100M.

Fig. 9.4:FTIR Spectrum of BET and Sodium bicarbonate

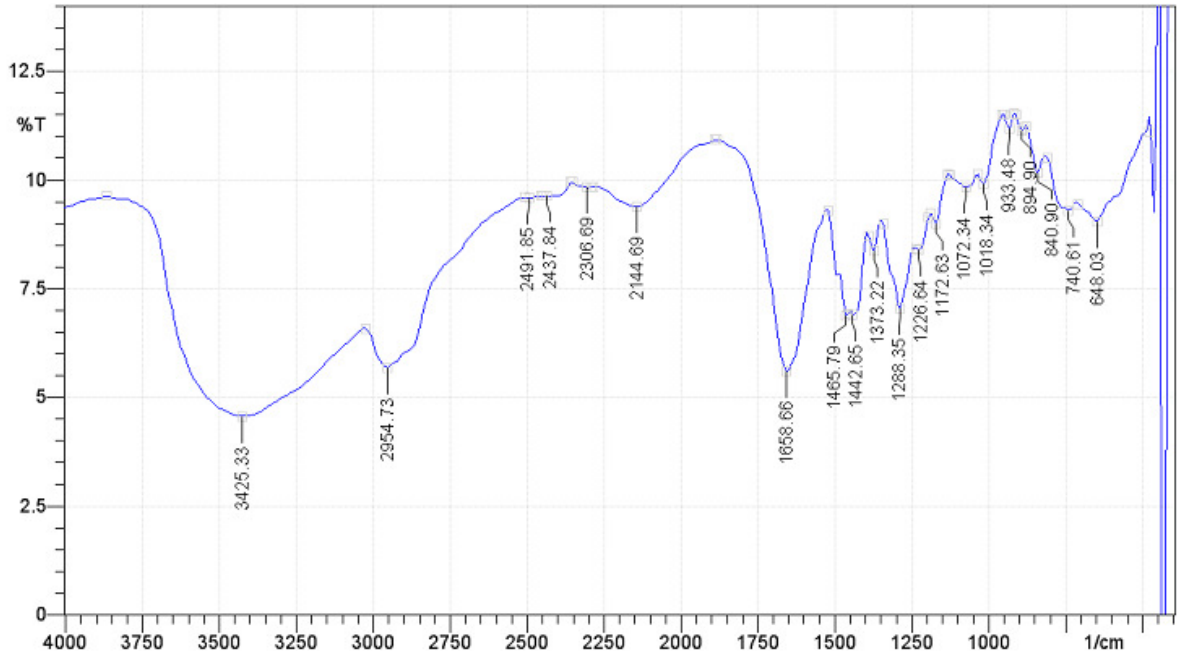


Tab. 9.5: FTIR Spectrum of BET and Sodium bicarbonate

Wave Number (cm^{-1})	Interpretation
3433	N-H Stretching
3008	C-H Stretching (aliphatic)
1627	C=C Stretching
1473	C-N Stretching

The peaks observed in the FTIR spectrum of BET HCl with Sodium bicarbonate showed no shift and no disappearance of characteristic peaks of drug. This suggests that there is no interaction between the drug and Sodium bicarbonate.

Fig. 9.5: FTIR Spectrum of BET HCl and PVP K30

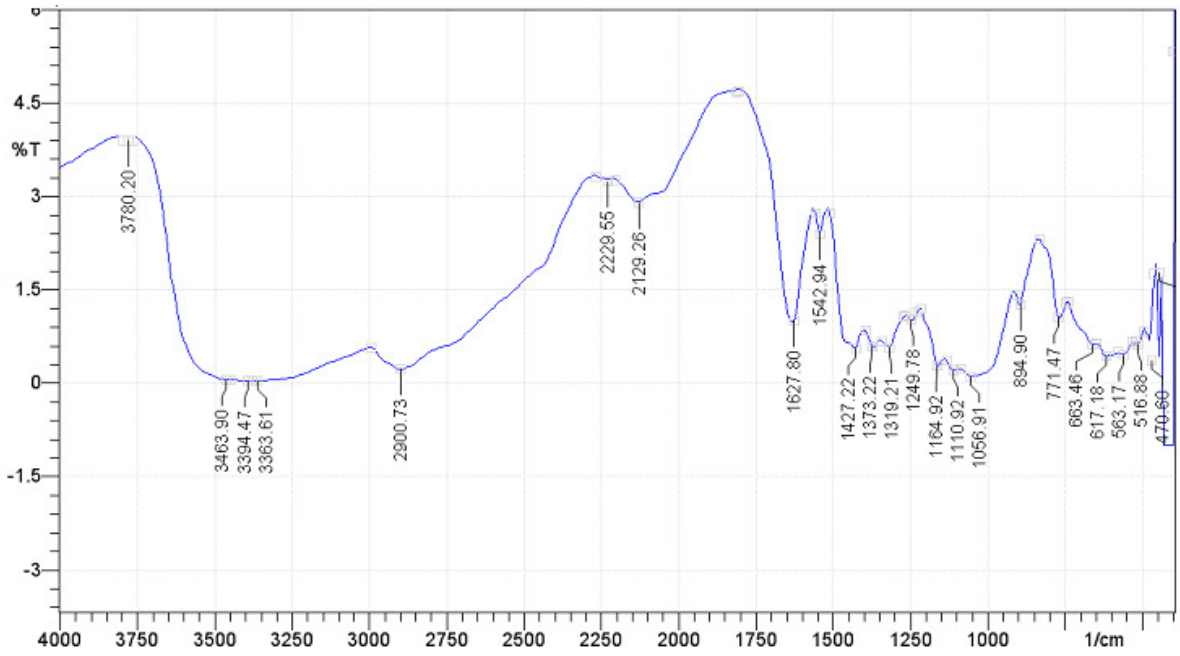


Tab. 9.6: FTIR Spectrum of BET HCl and PVP K30

Wave Number (cm^{-1})	Interpretation
3425	N-H Stretching
2954	C-H Stretching (aliphatic)
1658	C=C Stretching
1485	C-N Stretching

The peaks observed in the FTIR spectrum of BET HCl with PVP K30 showed no shift and no disappearance of characteristic peaks of drug. This suggests that there is no interaction between the drug and PVP K30.

Fig. 9.6: FTIR Spectrum of BET HCl and MCC

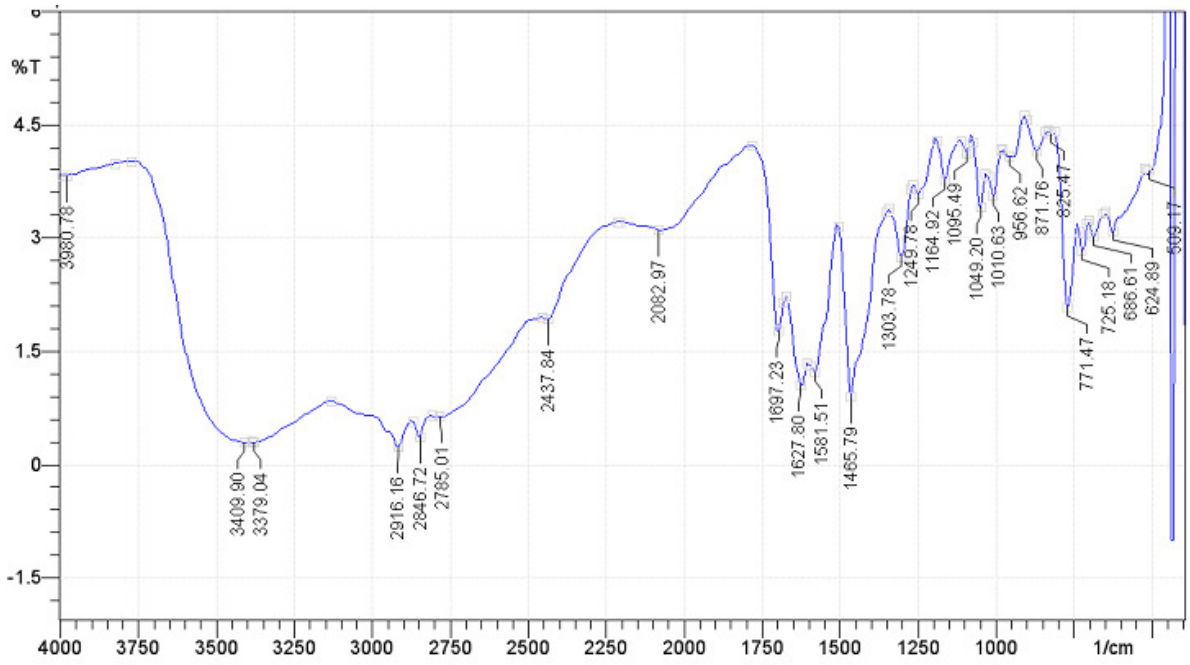


Tab.9.7: FTIR Spectrum of BET HCl and MCC

Wave Number (cm^{-1})	**Interpretation**
3394	N-H Stretching
2900	C-H Stretching (aliphatic)
1627	C=C Stretching
1427	C-N Stretching

The peaks observed in the FTIR spectrum of BET HCl with MCC showed no shift and no disappearance of characteristic peaks of drug. This suggests that there is no interaction between the drug and MCC.

Fig 9.7: FTIR Spectrum of BET HCl and Magnesium stearate



Tab. 9.8: FTIR Spectum of BET HCl and Magnesium stearate

Wave Number (cm^{-1})	Interpretation
3409	N-H Stretching
2916	C-H Stretching (aliphatic)
1697	C=C Stretching
1465	C-N Stretching

The peaks observed in the FTIR spectrum of BET HCl with Magnesium stearate showed no shift and no disappearance of characteristic peaks of drug. This suggests that there is no interaction between the drug and Magnesium stearate.

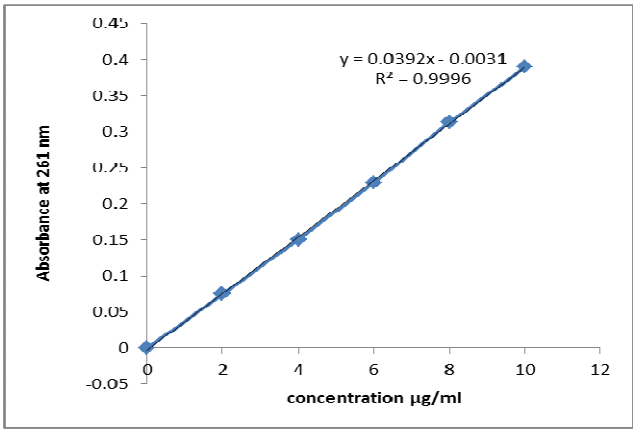
Standard Curve of Betahistine hydrochloride:

The absorbance of the drug in different concentrations in 0.1N Hydrochloric acid was measured at a wavelength of 261 nm. The results are given in Table 9.9. The standard curves plotted using the absorbance of various concentrations is shown in Figure 9.8

Tab. 9.9: Data for Standard curve of BET HCl

S.No	Concentration (µg/ml)	Absorbance at 261 nm
1.	0	0
2.	2	0.075
3.	4	0.150
4.	6	0.229
5.	8	0.313
6.	10	0.390

Fig. 9.8: Standard Curve of BET hydrochloride in 0.1N HCl



The standard curve is linear and starts from the origin. It obeys Beer – Lambert's law.

Precompression studies of the drug and powder blends:

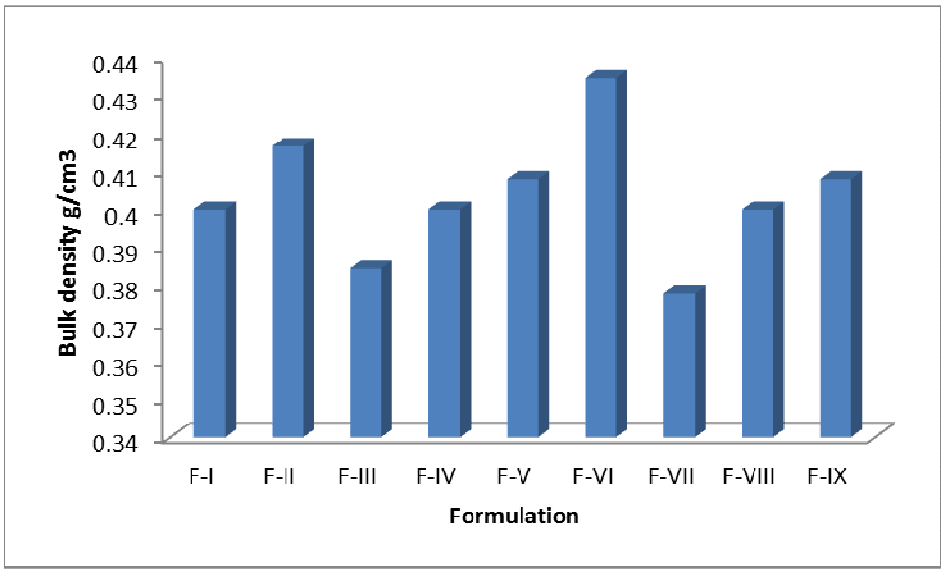
The results of the precompression study of the powder blends are given in Table 9.10 and Figures 9.9 to 9.13

.Tab.9.10: Precompression study of powder blends

Drug/ Powder blends	Bulk density* (g/cm^3)	Tapped density* (g/cm^3)	Compressibility index* (%)	Hausner's ratio*	Angle of Repose* (θ)
F-I	0.4000±0.047	0.5263±0.015	23.99±0.024	1.32±0.017	$30^0$03' ±0.054
F-II	0.4167±0.055	0.5556±0.032	25.00±0.038	1.33±0.009	$31^0$36'±0.026
F-III	0.3846±0.023	0.5000±0.067	23.08±0.016	1.30±0.025	$32^0$69'±0.054
F-IV	0.4000±0.041	0.5263±0.052	23.99±0.037	1.31±0.052	$31^0$98'±0.035
F-V	0.4081±0.016	0.5128±0.043	20.41±0.021	1.25±0.038	$32^0$60'±0.062
F-VI	0.4347±0.047	0.5556±0.068	21.76±0.059	1.27±0.027	$30^0$07'±0.028
F-VII	0.3778.±0.038	0.5000±0.016	24.44±0.028	1.32±0.045	$31^0$02'±0.063
F-VIII	0.4000±0.054	0.5263±0.047	23.99±0.015	1.32±0.029	$31^0$08'±0.037
F-IX	0.4081±0.019	0.5128±0.035	20.41±0.012	1.26±0.053	$32^0$21'±0.046

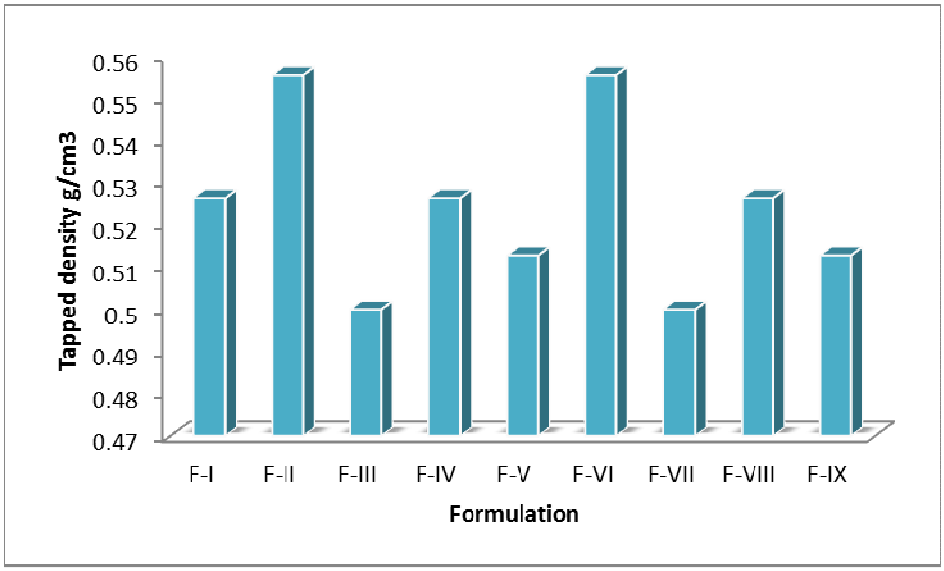
The drug blend has passable flow property. Hence, the tablets were prepared by wet granulation technique.

Fig. 9.9: Bulk density of powder blend



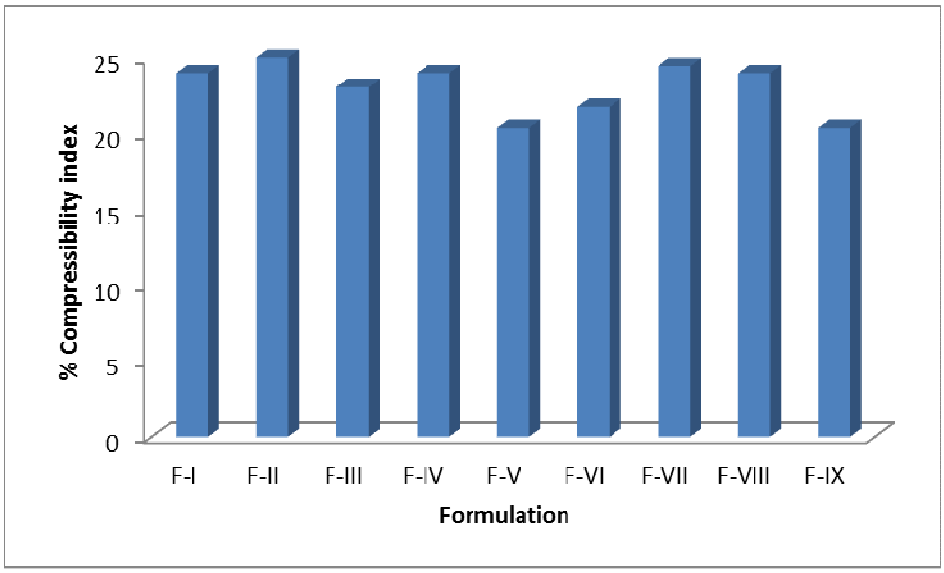
The bulk density of the powder blend of various formulations ranged from 0.3846 g/cm^3 to 0.4347 g/cm^3.

Fig. 9.10: Tapped density of powder blend



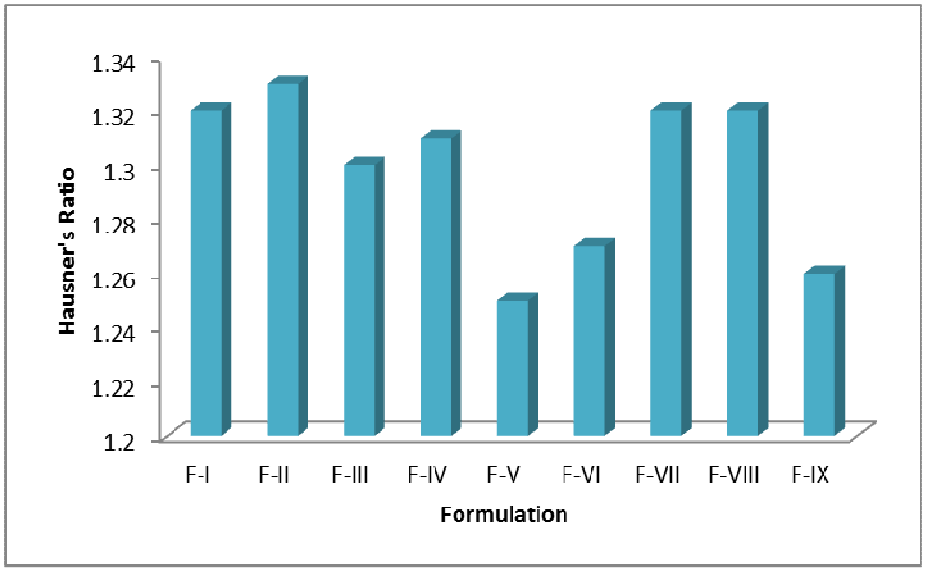
The tapped density of various formulations ranged from 0.5000 g/cm^3 to 0.5556 g/cm^3

Fig. 9.11: Compressibility Index of powder blend



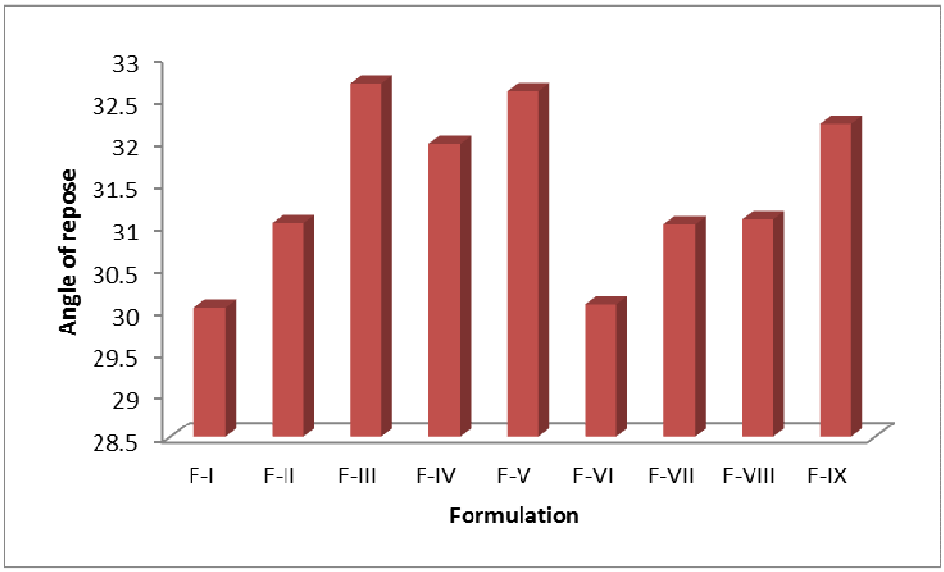
The compressibility index of various formulations ranged from 20.41% to 25.00% showing passable flow property. Hence wet granulation was used.

Fig. 9.12: Hausner's ratio of powder blend



The Hausner's ratio of various formulations ranged from 1.26 to 1.33 showing passable flow property.

Fig. 9.13: Angle of repose of powder blend



The angle of repose of various formulations ranged from $30^{0}03'$ to $32^{0}69'$ showing good flow property.

Evaluation of floating tablets:

1. Description:

The tablets were white coloured, round and flat faced with bevel – edged bisect.

2. Uniformity of Weight:

The tablets were tested for uniformity of weight and the results are given in Table 9.11

Tab.9.11: Uniformity of Weight of floating tablets

Formulation	Average Weight* (g)
F-I	0.3023±0.0015
F-II	0.3024±0.0053
F-III	0.3022±0.0026
F-IV	0.3034±0.0032
F-V	0.3040±0.0021
F-VI	0.3025±0.0039
F-VII	0.3017±0.0044
F-VIII	0.2952±0.0037
F-IX	0.2995±0.0018

*Mean±SD (n=3)

The weight of the tablets ranged from 0.2952 g to 0.3040 g. The tablets (F-I to F-IX) comply with the uniformity of weight test.[56]

3. Thickness:

Thickness of various formulations is given in Table 9.12.

Tab. 9.12: Thickness of floating tablets

Formulation	Thickness* (mm)
F-I	4.0±0.012
F-II	4.0±0.015
F-III	4.0±0.014
F-IV	4.0±0.016
F-V	4.0±0.012
F-VI	4.0±0.017
F-VII	4.0±0.004
F-VIII	4.0±0.0181
F-IX	4.0±0.015

*Mean±SD (n=3)

The thickness of the tablets is 4.00 mm. The tablets (F-I to F-IX) have uniform thickness.

4. Diameter:

Diameter of various formulations is shown in Table 9.13.

Tab. 9.13: Diameter of floating tablets

Formulations	Diameter* (mm)
F-I	9.5±0.0
F-II	9.5±0.0
F-III	9.5±0.0
F-IV	9.5±0.0
F-V	9.5±0.0
F-VI	9.5±0.0
F-VII	9.5±0.0
F-VIII	9.5±0.0
F-IX	9.5±0.0

*Mean±SD (n=3)

The diameter of the tablets is 9.5 mm. The tablets (F-I to F-IX) have uniform diameter.

5. Hardness:

The hardness of the floating tablets is given in Table 9.14.

Tab. 9.14: Hardness of floating tablets

Formulations	Hardness* (kg/cm^2)
F-I	4.3±0.2236
F-II	4.2±0.2236
F-III	4.0±0.1095
F-IV	4.2±0.1414
F-V	4.1±0.0894
F-VI	4.3±0.2236
F-VII	4.3±0.3536
F-VIII	4.0±0.2739
F-IX	4.3±0.2608

*Mean±SD (n=3)

The hardness of the tablets ranged from 4.0 kg/cm^2 to 4.3 kg/cm^2. The tablets (F-I to F-IX) have sufficient hardness to withstand transport and handling.

6. Friability:

The friability of various formulations is given in Table 9.15.

Tab. 9.15: Friability of floating tablets

Formulations	%Friability*
F-I	0.6869±0.032
F-II	0.5500±0.025
F-III	0.5100±0.016
F-IV	0.4012±0.027
F-V	0.4213±0.014
F-VI	0.5001±0.035
F-VII	0.5224±0.022
F-VIII	0.4991±0.011
F-IX	0.6057±0.018

*Mean±SD (n=3)

The percentage friability of various formulations ranged from 0.4012% to 0.6869%. The percentage friability is within the limit.[58]

7. Drug content:

The content of active ingredient in various formulations is given in Table 9.16.

Tab. 9.16: Drug content of tablets

Formulations	Drug content* (%w/w)
F-I	97.6±2.3126
F-II	98.1±1.5185
F-III	98.3±1.3809
F-IV	98.7±1.0251
F-V	97.1±1.1638
F-VI	97.2±0.9515
F-VII	107.2±0.6368
F-VIII	96.5±0.3609
F-IX	95.8±0.8991

*Mean±SD (n=5)

The percentage of drug content ranged from 96.32%w/w to 99.22%w/w. All the formulations comply with the official standards.[60]

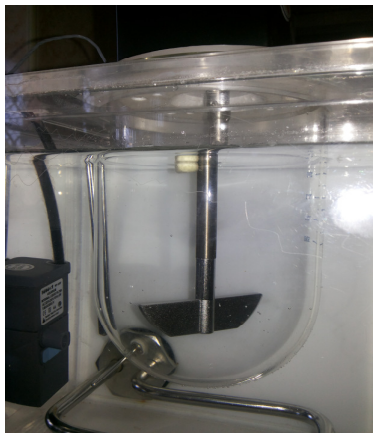
8. Swelling index

The swelling index of various formulations is given in Table 9.17

Formulations	Swelling index (%)
F-I	151
F-II	165
F-III	178
F-IV	167
F-V	176
F-VI	190
F-VII	175
F-VIII	183
F-IX	190

Fig. 9.14: floating lag time of tablets

a. At zero second **b. At 2 min 58 sec**



9. Buoyancy lag time and total floating time:

The buoyancy lag time and total floating time of various formulations are given in table 9.18 and fig.9.14

Tab. 9.18: Buoyancy lag time of floating tablets

Formulations	Buoyancy lag time (min)	Total floating time (hrs)
F-I	2 min 58 sec	>12
F-II	3 min 0 sec	>12
F-III	2 min 59 sec	>12
F-IV	2 min 51 sec	>12
F-V	2 min 45 sec	>12
F-VI	2 min 50 sec	>12
F-VII	2 min 54 sec	>12
F-VIII	2 min 38 sec	>12
F-IX	2 min 57 sec	>12

10. *In vitro* release study:

The results of *in vitro* release study are shown in Table 9.19- 9.21 and fig. 9.15-9.17

Tab. 9.19 : *In vitro* release study of tablets containing various concentrations of HPMC K4M

Time in hrs	Cumulative % drug release		
	F-I	F-II	F-III
0	0 ± 0.000	0 ± 0.0000	0 ± 0.0000
1	32.8 ± 0.3562	30.9 ± 0.2223	30.2 ± 0.5632
2	46.1 ± 0.1522	44.2 ± 0.3652	43.4 ± 0.2232
3	53.4 ± 0.2564	50.4 ± 0.5621	49.9 ± 0.5698
4	63.6 ± 0.3352	62.4 ± 0.8952	61.6 ± 0.5235
5	70.8 ± 0.5265	69.2 ± 0.5621	67.4 ± 0.5122
6	79.6 ± 0.5487	74.7 ± 0.5862	71.9 ± 0.5642
7	86.4 ± 0.5648	85.2 ± 0.2635	78.9 ± 0.5312
8	96.7 ± 0.3652	93.8 ± 0.5642	88.2 ± 1256
9		97.9 ±0.2682	96.5 ± 0.5164

Formulation F-I showed 96.7% drug release at the end of 8 hrs. The formulation F-II showed 97.9% drug release at the end of 9 hrs and the formulation F-III showed 96.5% drug release at the end of 9 hrs.

Tab. 9.20: *In vitro* release study of tablets containing various concentrations of HPMC K100M

Time in hrs	Cumulative % drug release		
	F-IV	F-V	F-VI
0	0 ± 0.0000	0 ± 0.0000	0 ± 0.0000
1	28.9 ± 0.1254	28 ± 0.1564	26.2 ± 0.0.5623
2	40.7 ± 0.5682	38.9 ± 0.5623	36.4 ± 0.2564
3	47.0 ± 0.4223	46.5 ± 0.2314	43.5 ± 0.3256
4	58.3 ± 0.5214	57.3 ± 0.2651	53.2 ± 0.3652
5	66.4 ± 0.1256	64.3 ± 0.2564	62.4 ± 0.5623
6	69.9 ± 0.5463	67.9 ± 0.4698	65.2 ± 0.5623
7	77.3 ± 0.5622	75.5 ± 0.5612	73.6 ± 0.5621
8	85.9 ±0.5642	84 ± 0.6125	81.1 ± 0.4120
9	93.7 ± 0.5312	93.3 ± 0.4562	88.8 ± 0.3256
10	97.4 ± 0.4622	96.4 ± 0.5622	93.5 ± 0.5478
11		98.8 ± 0.2563	96.1 ± 0.2356
12			99.0 ± 0.4622

Formulation F-IV showed 97.4% drug release at the end of 10 hrs. The formulation F-V showed 98.8% drug release at the end of 11 hrs and the formulation F-VI showed 99.0% drug release at the end of 12 hrs.

Table 9.21: *In vitro* release study of tablet containing various concentration of HPMC K4M and HPMC K100M

Time in hrs	Cumulative % drug release		
	F –VII	**F –VIII**	**F - IX**
0	0 ± 0.0000	0 ± 0.0000	0 ± 0.0000
1	29.9 ± 0.5224	28.7 ± 0.4522	28.2 ± 0.2563
2	42.6 ± 0.5456	41.3 ± 0.1562	38.6 ± 0.3652
3	48.9 ± 0.6582	47.9 ± 0.2112	47.1 ± 0.4552
4	58.9 ± 0.2541	56.4 ± 0.3562	56.1 ± 0.2589
5	65.8 ± 0.4562	67.2 ± 6853	63.6 ± 0.2456
6	70.9 ± 0.6524	72.7 ± 0.4562	67.1 ± 0.3654
7	81.7 ± 0.5452	77.5 ± 0.3256	76.1 ± 0.1256
8	89.7 ± 0.5641	85.6 ± 0.3652	85.2 ± 0.2564
9	97.3 ± 0.4521	93.3 ± 0.3425	93.6 ± 0.2254
10		98.4 ± 0.5461	96.9 ± 0.2561
11			99.2 ± 0.1546

Formulation F-VII showed 97.3% drug release at the end of 9 hrs. The formulation F-VIII showed 98.4% drug release at the end of 10 hrs and the formulation F-IX showed 99.2% drug release at the end of 11 hrs.

Fig.9.15: Cumulative percentage drug release of formulation F-I, F-II and F-III

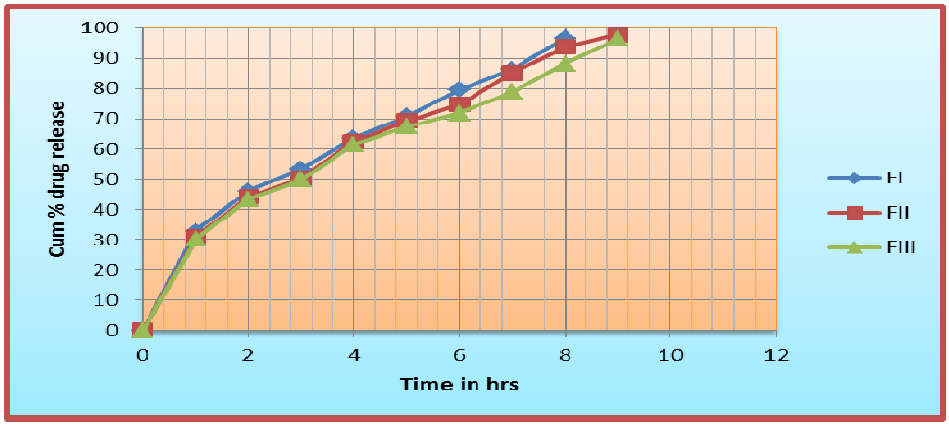
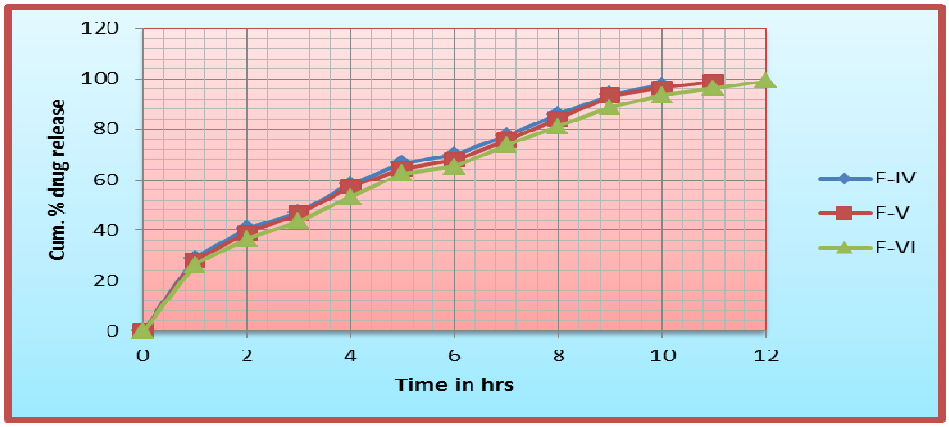
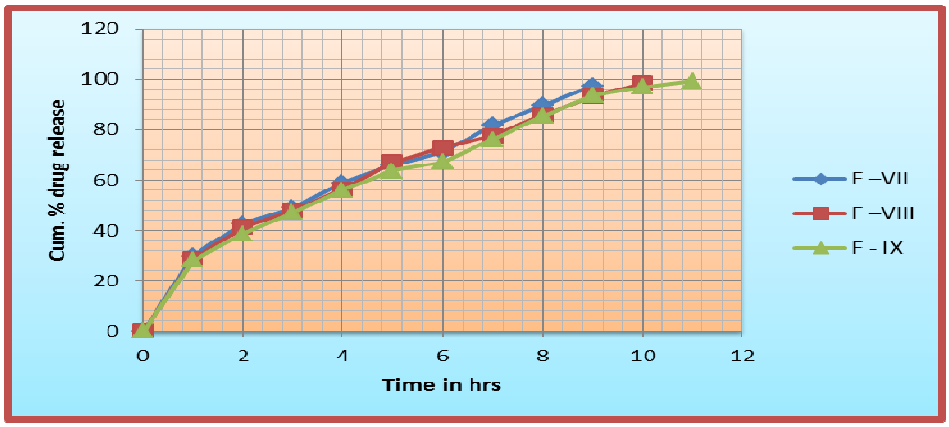


Fig.9.16: Cumulative percentage drug release of formulation F-IV, F-V and F-VI



Fig; 9.17: Cumulative percentage drug release of formulation F-VII, F-VIII and F-IX



Tab. 9.22: Release kinetics of the optimized formulation

Time in hrs	% cumulative drug release	% cumulative drug remaining	log % cumulative drug release	Square root of time	Log time	log % cum drug remaining	cube root of % drug remaining
0	0	100	-α	0	-α	2	4.6415
1	26.2	73.8	1.4183	1	0	1.8680	4.1945
2	36.4	63.6	1.5611	1.4142	0.3010	1.8034	3.9916
3	43.5	56.5	1.6384	1.73205	0.4771	1.7520	3.8372
4	53.2	46.8	1.7259	2	0.6020	1.6702	3.6036
5	62.4	37.6	1.7951	2.2360	0.6989	1.5751	3.3501
6	65.2	34.8	1.8142	2.4494	0.7781	1.5415	3.2648
7	73.6	26.4	1.8668	2.6457	0.8450	1.4216	2.9776
8	81.1	18.9	1.9090	2.8284	0.9030	1.2764	2.6637
9	88.8	11.2	1.9484	3	0.9542	1.0492	2.2373
10	93.5	6.5	1.9708	3.1622	1	0.8129	1.8662
11	96.1	3.9	1.9827	3.3166	1.0413	0.5910	1.574
12	99	1	1.9956	3.4641	1.0791	0	1

Fig 9.18: Plot of Zero Order Release Kinetics

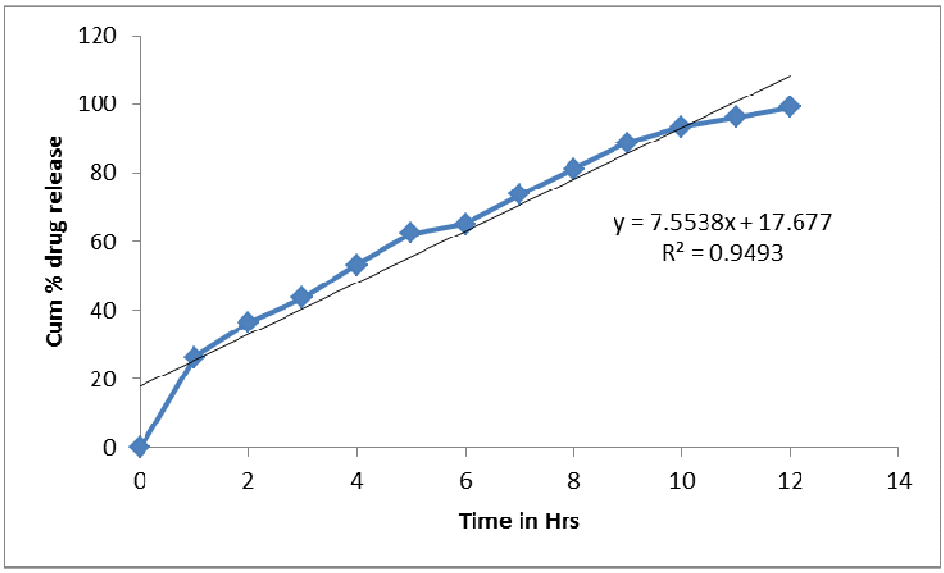


Fig. 9.19: Plot of First Order Release Kinetics

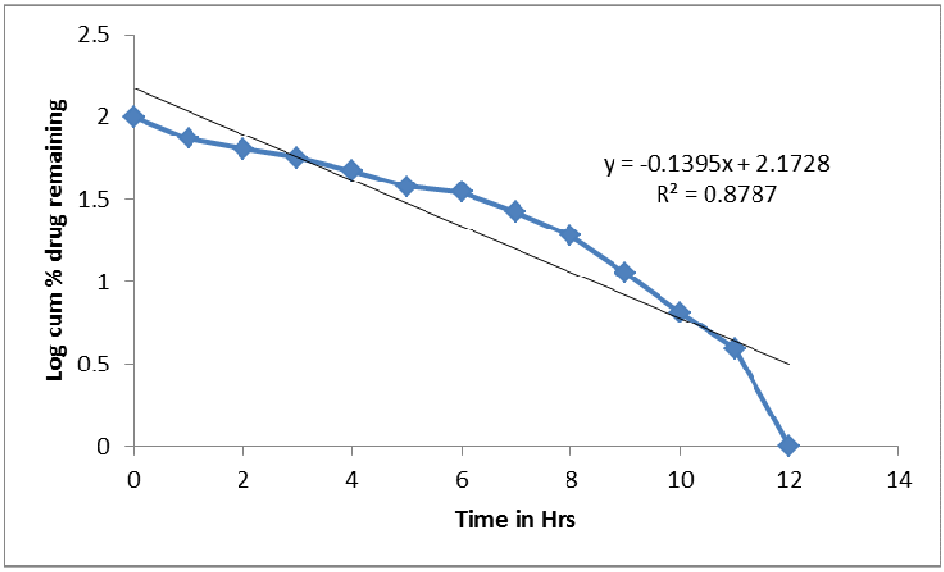


Fig 9.20: Plot of Higuchi Kinetics

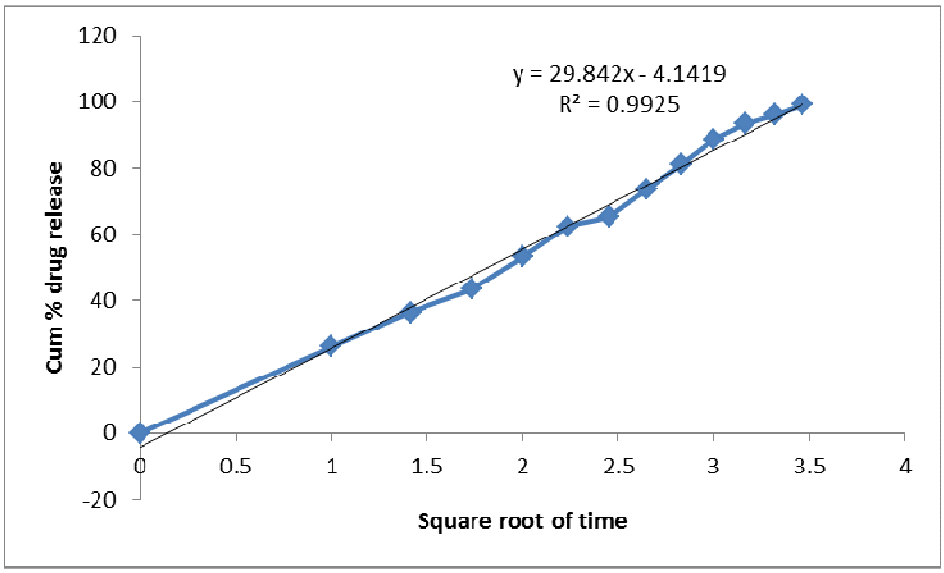


Fig.9.21: Plot of Korsemeyer Peppas Kinetics

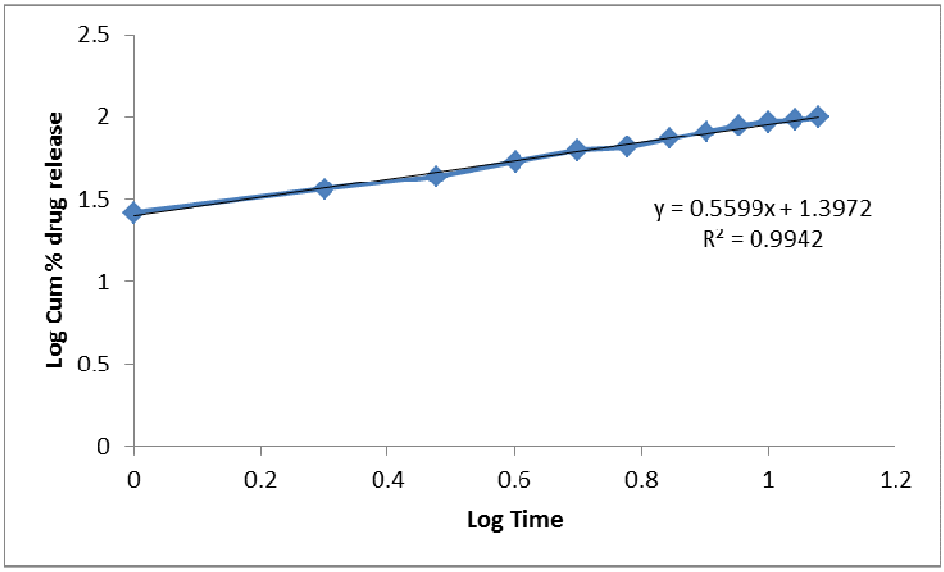
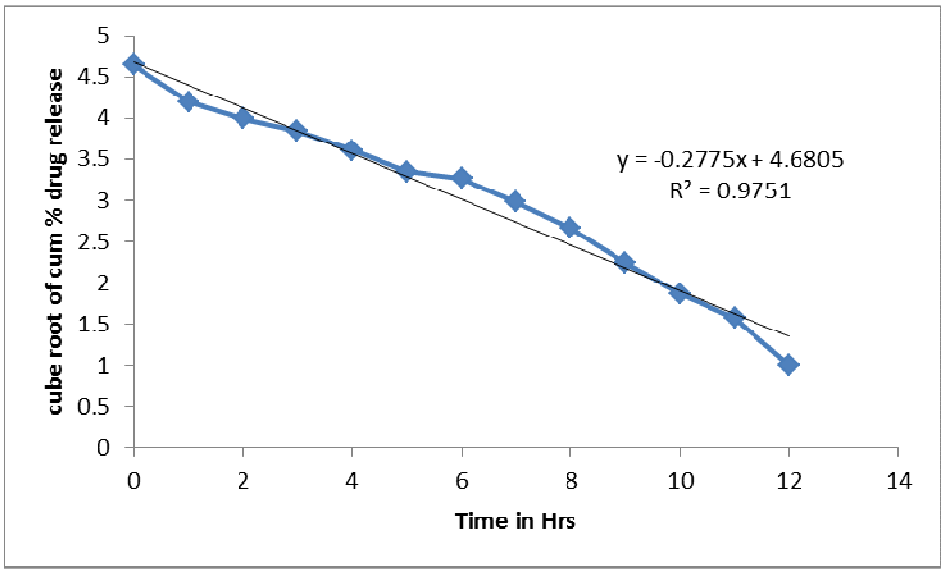


Fig. 9.22: Plot of Hixson – Crowell Kinetics



The plot of determination (R^2) was taken as criteria for choosing the most appropriate model. The R^2 values of various kinetic models are given in Table 9.23.

Table 9.23: R^2 values of various kinetic models

Kinetic model	**Coefficient of determination** (R^2)
Zero order	0.9493
First order	0.8787
Higuchi	0.9925
Korsmeyer and Peppas	0.9942
Hixson – Crowell	0.9751

Among the various plots, it was clear that Zero order equation showed good linearity (R^2 =0.9493). Therefore in the present study, the *in vitro* release profiles of Betahistine were best described by Zero order release model followed by Korsemeyer – Peppas kinetics. The

diffusion exponent of the solute n is 0.5599. Hence, the mechanism of drug release was found to be Anomalous non fickian transport.

Stability studies

The stability study results of optimized formulation is given in table 9.24

Tab.9.24: Stability of optimized formulation (F-VI)

S.No	Temperature 40±2°C and RH 75±5%			
	Parameter	**Month 1**	**Month 2**	**Month 3**
1	Uniformity of weight (g)	0.3025±0.0047	0.3021±0.0024	0.3019±0.0056
2	Thickness (mm)	4.0±0.017	4.0±0.0151	4.0±0.0251
3	Diameter (mm)	9.5±0.0	9.5±0.0000	9.5±0.0000
4	Hardness (kg/cm^2)	4.3±0.2236	4.2±0.1256	4.4±0.2546
5	% friability	0.5001±0.035	0.4985±0.015	0.5142±0.1256
6	Floating lag time	2 min 50 sec	2 min 45 sec	2 min 58 sec
7	Total floating time	>12 hrs	>12 hrs	>12 hrs
8	Drug content (% w/w)	97.2±0.9515	97.4±0.8568	97.0±0.5623
9	*In vitro* drug release at the end of 12 hrs (% w/w)	98.0 ± 0.4622	97.9±0.5642	98.4±0.2315

From the above results, it is observed that the optimized formulation maintains the stability for 3 months.

10. SUMMARY AND CONCLUSION

SUMMARY

The Betahistine hydrochloride was successfully formulated into controlled release floating tablets using various grades of matrix-forming polymer such as HPMC K4M, HPMC K100M and its combination by wet granulation method.

- Preformulation studies were performed for powder blends.
- Physical compatibility study showed that the drug and excipients are physically compatible with each other.
- Chemical compatibility study was performed using FTIR spectroscopy and FTIR studies revealed that there was no change in major peaks thus confirming no interaction between the drug and excipients.
- Betahistine hydrochloride powder blend had passable flow property which was substantiated by bulk density, tapped density, compressibility index, Hausner's ratio and angle of repose. Hence, the floating tablets of Betahistine hydrochloride were prepared by wet granulation method.
- The post compression parameters of tablets were evaluated and the results were found to comply within limit.
- The buoyancy lag time of all formulations were less than 3 min.
- The total floating time of all formulations were more than 12 hrs.
- The *in vitro* release studies were performed for all the formulations. Formulation F-VI containing 60% of HPMC K 100 M released 99.0% at the end of 12 hrs. Therefore, F-VI was chosen as the optimized formulation.
- The dissolution data of the optimized formulation were fitted to various kinetic models and the formulation F-VI fitted best to Zero order release kinetics. The mechanism of drug release was found to be diffusion, dissolution and swelling.

From the overall results, it is clear that the formulation F-VI containing 60% of HPMC K 100 M is the optimal formulation among the other formulations, as it produced controlled drug release than other formulations.

CONCLUSION

- The floating tablets of Betahistine hydrochloride may be useful over conventional system for effective treatment of vertigo in Meniere's disease.
- The floating tablets of Betahistine hydrochloride may be administered twice daily instead of four times a day.

FUTURE SCOPE

- Long term Stability studies for the optimized formulation as per the current ICH guidelines.
- Pharmacokinetic and toxicity study.
- Scale up studies for the optimized formulation.

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